journal of

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THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING APRIL AND MAY, 1950

LONDON.

Thursday, May 4th, 1950, at 7.15 p.m.

Tilden Lecture, **Recent Advances in the Chemistry of the Steroids,** by Professor F. S. Spring, D.Sc., F.R.I.C.

To be given at the Royal Institution, Albemarle Street, W.1.

BIRMINGHAM.

Friday, May 5th, 1950, at 4.30 p.m.

Lecture, **The Shape of a Chemical Bond,** by Professor C. A. Coulson, M.A., D.Sc.

Joint meeting with the University Chemical Society to be held in the Main Chemistry Lecture Theatre, The University, Edgbaston, Birmingham.

NORTH WALES.

Thursday, May 4th, 1950, at 5.30 p.m.

Lecture, **Light-scattering and Chemistry,** By Dr. E. J. Bowen, M.A., F.R.S.

Joint meeting with University College of North Wales Chemical Society to be held in the Department of Chemistry, University College of North Wales, Bangor.

ST. ANDREWS AND DUNDEE.

Thursday, April 6th, 1950, at 5.15 p.m.

Lecture, **Chemical Reactions Induced by Nuclear Radiations,** by Dr. F. S. Dainton, M.A.

To be given in the Chemistry Lecture Theatre, University College, Dundee.

(Note: Not April 13th as previously announced.)

Friday, April 7th, 1950, at 5.15 p.m.

Lecture, **Developments in the Chemistry of *cyclo*Heptane Derivatives,** by Professor R. D. Haworth, D.Sc., F.R.S.

Joint meeting with St. Andrews University Chemical Society to be held in the Chemistry Department, United College, St. Andrews.

SHEFFIELD.

Thursday, April 27th, 1950, at 5.30 p.m.

Tilden Lecture, **Recent Advances in the Chemistry of the Steroids,** by Professor F. S. Spring, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Sheffield.

SOUTHAMPTON.

Wednesday, April 26th, 1950, at 7 p.m.

Lecture, **Trace Elements in Plant Life,** by Dr. W. A. Roach, A.R.C.S., A.R.I.C.

Joint meeting with Mid-Southern Counties Section of the Royal Institute of Chemistry and Portsmouth and District Chemical Society, to be held at the Municipal College, Portsmouth.

Friday, May 5th, 1950, at 5 p.m.

Lecture, **Recent Synthetical Developments in Pyrethrum Chemistry,** by Dr. S. H. Harper, A.R.C.S., D.I.C.

Joint meeting with University College of Southampton Chemical Society, to be held in the Physics Department, University College, Southampton.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at the Royal Institution, Albemarle Street, W.1, on Thursday, January 19th, 1950, at 7.15 p.m.

The President, SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on Thursday, December 15th, 1949, were read, and were confirmed and signed.

VACANCIES ON COUNCIL 1950—1951.

The notice regarding vacant places on Council, due to be filled at the Annual General Meeting to be held in Edinburgh on March 29th, 1950, was read.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: D. B. Freeman, J. D. Butler, Roy R. Bishop, M. F. Fletcher, D. T. King, F. S. Dainton, L. F. Oldfield, D. A. Andrews, J. W. Linnett, Thos. D. Brogan, J. A. Saunders, E. G. Jefferson, D. Bennion, L. Dewhirst, J. Stuart-Webb, James Daly.

TILDEN LECTURE.

After a brief introduction, the President called upon Professor M. G. Evans, F.R.S., to deliver the Tilden Lecture entitled, "Studies on Electron-transfer Reactions."

At the conclusion of the Lecture, Professor C. E. H. Bawn proposed a vote of thanks to Professor Evans which was carried with acclamation.

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, February 2nd, 1950, at 7.15 p.m.

The President, SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held on January 19th, 1950, at the Royal Institution, Albemarle Street, London, W.1, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: J. Sutton, C. B. Amphlett, J. Wright, Sidney Landsman, D. S. Papworth, A. J. Swallow, R. D. Mulley, E. M. Fenn, J. E. Humpoletz, I. G. Ross.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed :

" The Structure of Molecular Compounds," by H. M. Powell.
Part VII. Compounds formed by the inert gases.
Part VIII. The compound of krypton and quinol.

" Chemical Actions of Ionising Radiations on Aqueous Solutions," by G. Stein and J. Weiss.
Part I. Introduction and description of irradiation arrangements (with F. T. Farmer).
Part II. The action of *X*-rays on benzene and benzoic acid.
Part III. The action of neutrons and of alpha-particles on benzene.
Part IV. The action of *X*-rays on some amino-acids.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows :

	Elected.	Died.
Charles Edwin Barton (Northwood Hills) ...	Dec. 2nd, 1937.	Dec. 12th, 1949.
Albert Edward Gillam (Manchester) (C. 1948—)	May 7th, 1936.	Jan. 16th, 1950.
Herbert Edwin Jones (Northwich)	July 9th, 1946.	Oct. 10th, 1949.
Harold Marmion Royle (Southend-on-Sea)...	Dec. 7th, 1905.	Aug. 24th, 1949.

ELECTION OF NEW FELLOWS.

The following 52 candidates were elected Fellows of the Society on January 19th, 1950 :

James Arthur Raymond Bates.
Eileen Loraine Blackall.
Sidney Frank Brailsford.
Richard Charles Braun.
John Henry Brookman.
Sidney Maurice Budd.
Jayarajan Chanmugam.
John Russell Clarke.
John Cameron Clunie.
John Samuel Collins.
Hazel Ginette Corbet.
Stanley Jerome Cristol.
George Eric Derome.
James Forest.
Edward Malcom Fenn.
Norman G. Gaylor.
Gordon Merrick Hankinson.
John Marion Hartog.
Eric William Hasler.
Raymond Hemming.
Keith John Heritage.
Arthur Kenneth Holliday.
Sheila Mary Hollingworth.
Phillip Reid Jefferies.
Thomas Henry Kennedy.
Michael Joseph Kenney.
Ai Kim Kiang.
Erik Larsson.
John Trevor Law.
Walter Henry Lee.
Betty Florence Maude London.
Alan Peter MacKenzie.
Florence June Macrae.
Betty Margaret Marshall.
Peter Charles Merriman.
William Allison Mosher.
Derek William Ockenden.
Mrs. Eva Maria Philbin.
Jack Watson Rasburn.
John Rich.
Edward John Sparks.
Leslie John Spencer.
Hugo Stange.
Robert Stevenson.
Victor Raymond Stimson.
Dennis Thompson.
Ronald Austin Thompson.
Erica Weiss.
Kenneth Berle Wiberg.
Clarence Williams.
James Michell Williams.
John Radford Wilson.

MEETING OF COUNCIL.

A Meeting of Council was held on January 19th, 1950.

The Council stood as a tribute to the memory of Dr. A. E. Gillam, Member of Council since 1948, whose death was reported.

The report of the meeting of the Publication Committee on December 15th, 1949, was adopted.

Acknowledgment was made to the Royal Society for a further grant of £200 from the Scientific Publications Grant-in-Aid towards the cost of publications for 1949.

The Council noted that printing charges had been further increased by 5 per cent. as from the beginning of the year.

It was noted with satisfaction that Mr. W. A. Bush of Los Angeles had made a donation of £3 10s. 0d., the amount overpaid when remitting his annual subscription, and Council gave instructions for the following extract from his letter to be published:

> "I shall be much obliged to you (assuming that when all of these services are taken into consideration, I have overpaid) if you will kindly plow the amount of the overpayment into the Society's general funds. I think most of us members are still getting more than our money's worth and I know that I shall be happy to throw a little extra into the 'kitty.'"

A further grant from the Research Fund was authorised, Mr. R. C. Braun (Hendon Technical College) being awarded £35 for a research entitled, "The Rate of Solution of Sodium Chloride in Liquid Solvents."

QUARTERLY REVIEWS VOLUMES I—III.

Fellows are reminded that all three volumes of the *Quarterly Reviews*, 1947—1949, are obtainable from the General Secretary at £1 10s. 0d. per volume less Fellows' discount of 15 per cent.

NOMINATIONS FOR VACANT PLACES ON COUNCIL, 1950—1951.

The following is the list of nominations for vacant places on the Council which are due to be filled at the Annual General Meeting on March 29th, 1950.

President.

PROFESSOR E. K. RIDEAL (London).

Vice-President, who has not filled the Office of President (*One Vacancy.*)

PROFESSOR G. R. CLEMO	(Newcastle-upon-Tyne).
PROFESSOR M. G. EVANS	(Manchester).
PROFESSOR R. P. LINSTEAD	(London).
SIR JOHN SIMONSEN	(London).

Elected Ordinary Members of Council.

Constituency I. (South-East England.) (*Two Vacancies.*)

DR. J. S. ANDERSON	(Harwell).
DR. ISHBEL G. M. CAMPBELL	(Southampton).
DR. J. CHATT	(Welwyn).
DR. L. N. OWEN	(London).
PROFESSOR GWYN WILLIAMS	(London).

Constituency IV. (North-East England.) (*Two Vacancies.*)

PROFESSOR L. HUNTER	(Leicester).
PROFESSOR F. E. KING	(Nottingham).
DR. R. RAPER.	(Durham).
DR. T. S. STEVENS	(Sheffield).

Ballot papers have been dispatched to Fellows.

RESEARCH FUND.

A meeting of the Research Fund Committee will be held in June next.

Applications for Grants, to be made on forms obtainable from the General Secretary, must be received on or before May 1st, 1950. Applications from Fellows will receive prior consideration.

Attention is drawn to the fact that the income arising from the Donation of the Worshipful Company of Goldsmiths is principally devoted to the encouragement of research in Inorganic and Metallurgical Chemistry, and that the income from the Perkin Memorial Fund is to be applied to investigations relating to problems connected with the Coal Tar and Allied Industries.

HARRISON MEMORIAL PRIZE.

In accordance with the Trust Deed governing the Harrison Memorial Fund, the Selection Committee, consisting of the Presidents of the Chemical Society, the Royal Institute of Chemistry, the Society of Chemical Industry, and the Pharmaceutical Society, will proceed to make an award of the Harrison Memorial Prize in December 1950, subject to the condition that the Selection Committee shall be of opinion that there is a candidate of sufficient distinction to warrant an award of the Prize.

The Prize, not exceeding £150, will be awarded to the chemist of either sex, being a natural-born British subject and not at the time over thirty years of age, who, in the opinion of the Selection Committee, shall, during the previous five years, have conducted the most meritorious and promising original investigations in Chemistry and published the results of those investigations in a scientific periodical or periodicals.

Applications, five copies of which must be submitted, should give the name of the applicant (in full); age (birth certificate must accompany the application); degrees (with name of University); any other qualifications and experience; titles of published papers (with co-authors names) including full references to publication; where research was carried out; testimonials and references; and any other particulars bearing on the application.

The Selection Committee is prepared to consider applications, nominations, or information as to candidates eligible for the Prize. Any such communication must be received by the President, The Chemical Society, Burlington House, Piccadilly, London, W.1, *not later than Friday, December* 1*st*, 1950. Candidates must not have attained the age of thirty years at this date.

LIBRARY.

The Library will close for the Easter holiday at 1 p.m. on Thursday, April 6th and re-open at 10 a.m. on Wednesday, April 12th, 1950.

MEETINGS OUTSIDE LONDON.

BIRMINGHAM.

"The Separation and Determination of the Sugars and their Derivatives," by Dr. J. K. N. Jones, M.Sc., A.R.I.C.

A joint meeting with the University Chemical Society was held in the Chemistry Department of the University on January 20th, 1950, with Professor M. Stacey in the Chair.

The Lecturer gave a brief description of the classical methods employed for the characterisation and determination of the sugars and of their derivatives. These methods are dependent upon either the presence of reducing aldehydic, or ketonic, groupings or the formation of a derivative of furan and its subsequent detection as a coloured compound.

The application of paper-partition chromatography to the separation and determination of the sugars on the micro- and semi-micro scale was then described. This process has greatly facilitated the separation, identification, and determination of the sugars and of their derivatives. The separated sugars may be determined by colorimetric or by titration methods. It was shown that sugar mixtures could be separated by partition chromatography on columns of cellulose, the eluate being collected by means of an automatic fraction-collecting machine. The application of this new analytical method to various carbohydrate problems was described.

An interesting discussion followed the lecture, after which a vote of thanks, proposed by Dr. E. J. Bourne, was carried with enthusiasm.

EBINBURGH.

Display of Scientific Films.

A joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry was held in the Young Men's Christian Association Hall, St. Andrews Street, Edinburgh, on December 8th, 1949, with Mr. R. G. Thin, F.R.I.C., in the Chair.

A number of interesting scientific films were shown and included "Crystal Growth," "The Discovery of a New Pigment," "Colour," "Radar Record," "The Nature of Plastics," and "The Manufacture of Whisky."

The meeting concluded with a vote of thanks to Dr. G. Barclay for arranging the meeting.

"The Deflocculation of Long-fibred Pulps by Mucilages," by Dr. H. Ainsworth Harrison, M.Sc., F.R.I.C.

A joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry was held in the North British Station Hotel on January 19th, 1950, with Professor S. J. Watson in the Chair.

Dr. Harrison described entertainingly the significance and potentiality of using gums in paper manufacture, and illustrated his remarks by exhibiting many samples and specimens. A lively discussion terminated with a vote of thanks moved by Dr. K. F. MacBean.

"The Reactions of Carbon Monoxide and Oxygen on Copper Oxide," by Professor W. E. Garner, C.B.E., F.R.S.

A joint meeting with the Local Sections of the Royal Institute of Chemistry and the Society of Chemical Industry and the Edinburgh University Society was held in the Biochemistry Lecture Theatre of the University on February 7th, 1950, with Mr. A. A. Woodham in the Chair.

Professor Garner gave a most interesting account of how the results obtained by himself and his collaborators are interpreted in terms of modern theory. A vote of thanks, moved by Dr. C. F. H. Tipper and seconded by Professor J. P. Kendall, F.R.S., was carried with acclamation.

IRISH REPUBLIC.

"The Cortisone Problem," by Professor E. R. H. Jones, D.Sc., F.R.I.C.

A meeting was held in the Chemistry Lecture Theatre, University College, Upper Merrion Street, Dublin, on January 11th, 1950, with Dr. V. C. Barry in the Chair.

Professor Jones stated that during the past year information has become available concerning the successful treatment of rheumatoid arthritis with a steroid hormone known variously under the names of 17-hydroxy-11-dehydrocorticosterone, Kendall's Compound E, or Cortisone. This hormone is one of the twenty-eight crystalline substances which have been isolated from the adrenal cortex during the past twelve years as a result of the remarkable investigations of Kendall, Reichstein, Wintersteiner, and Pfiffner, and their collaborators. It can be isolated only in minute quantities from natural sources, but the treatment, on the other hand, requires the continued administration of at least 100 mg. per day. It has only been made available for clinical trials as a result of a most gallant piece of synthetic work by Sarett, who obtained it from deoxycholic acid by a procedure involving more than thirty consecutive steps in an overall yield of the order of 0·1 per cent.

The various stages involved in the partial synthesis of cortisone were discussed, and several directions in which the solution to the cortisone problem might be sought were indicated. These include the possibility of partial synthesis from other naturally occurring steroids, *e.g.*, sarmentogenin obtained from the seeds of the tropical vine *Strophanthus*

sarmentosus. The influence of structural features on the arthritic activity of cortisone-like molecules and the possibility of total synthesis were also examined.

It is known that an extract of the anterior lobe of the pituitary gland, the adreno-corticotrophic hormone (ACTH), which presumably activates the adrenal gland to produce cortisone, is also effective in relieving arthritic symptoms. This hormone, which is known to be of a protein-like nature, has been degraded by Li by hydrolysis with pepsin, and active dialysable fragments retaining considerable adrenal-stimulating activity are produced. These fragments contain on an average about seven peptide units, and it is likely that information concerning the constituent amino acids and their sequence will be forthcoming in the not too distant future. The solution of the cortisone problem may follow the synthesis of such peptides.

An interesting discussion followed the lecture, and the thanks of the meeting were conveyed to Professor Jones by the Chairman.

LIVERPOOL.

"The Biological Oxidation of Certain Aromatic Compounds with Special Reference to the Bacterial Cleavage of the Benzene Ring," by Dr. W. C. Evans.

A meeting was held in the Chemistry Lecture Theatre of the University on December 15th, 1949, with Professor R. A. Morton in the Chair.

The appreciation of the audience was demonstrated by the lengthy and vigorous discussion which followed. A vote of thanks, proposed by Dr. R. J. S. Beer, was carried with acclamation.

NORTH WALES.

"Some Aspects of the Chemistry of Simple Peptides," by Professor F. E. King, M.A., D.Sc.

A joint meeting with University College of North Wales Chemical Society was held at Bangor on February 2nd, 1950, with Mr. S. J. Pirt in the Chair.

Following a brief consideration of the chemical nature of peptides and synthetic methods devised by Emil Fischer, Professor King went on to describe the advantages of the carbobenzyloxy- and phthalic anhydride methods of synthesis, particularly in respect of peptides containing dibasic acid residues. The syntheses of α-peptides, such as glutamine, were outlined. The folic acid series of growth factors were discussed, and their relationships to pteroic acid derivatives were explained. The characteristics and attempted syntheses of the peptide from anthrax bacillus, of strepogenin, and of lycomarasmin were described.

An enthusiastic vote of thanks was accorded on the call of Dr. F. H. Newth.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the Journal *for February, 1950. Such objections will be treated as confidential. The forms of application are available in the Library.)*

Alcock, Margaret. British. 10, Dovedale Avenue, Droylsden, Manchester. Research Chemist at Thomas Kerfoot & Co., Ltd., Ashton-under-Lyne. *Signed by :* D. M. Lever, E. Whalley, L. E. Martin.

***Anderson, Joan Audrey,** B.Sc. (Lond.). British. 27, Woodville Gardens, Ealing, W.5. Micro-biologist. *Signed by :* D. W. Kent-Jones, G. B. Thackray, R. A. Knight.

***Allerton, Roy,** B.Sc. (Birm.). British. 101, Oakfield Road, Selly Park, Birmingham, 29. Research Student at Birmingham University. *Signed by :* L. L. Bircumshaw, W. G. Overend, P. W. Kent.

Beesley, Jack Antony, B.Sc. (Birm.), A.R.I.C. British. 19, Southwick Street, W. 2. Senior Chemist at Messrs. J. Lyons & Co., Ltd., W.14. *Signed by :* J. H. Bushill, D. H. Clayson, J. C. Baker.

***Bell, Ernest Arthur,** B.Sc. (Dunelm.), A.R.I.C. British. Department of Biochemistry, Trinity College, Dublin. University Lecturer. *Signed by :* C. Lipman, W. Cocker, K. C. Bailey.

Bell, Jack Gorman, B.Sc. (Lond.). British. 15, Grosvenor Road, Haydock, Lancs. Church of England Lay Worker. *Signed by :* J. McLintock, A. Walton, L. A. Haddock.

***Beton, June Annette,** B.Sc. (Manc.). British. 29, Norman Road, Sale, Manchester. Research Chemist. *Signed by :* I. E. Balaban, B. E. Wilde, J. A. Calderwood.

***Brown, Henry.** British. 82, Lowerhouse Lane, Burnley, Lancs. Student. *Signed by :* A. Walton, J. E. Wynfield Rhodes, V. G. Jolly.

Clark, Edward Raymond, B.Pharm. (Wales), Ph.D. (Lond.), A.R.I.C. British. Department of Organic Chemistry, The University, Leeds, 2. Assistant Lecturer. *Signed by :* J. W. Baker, E. Rothstein, F. Challenger.

***Cole, Donald John.** British. 71, Primrose Avenue, Chadwell Heath, Romford. Research Chemist. *Signed by :* A. E. Lilly, D. M. Page, E. F. G. Thorpe.

***Cole, Sylvia Louise,** B.A. (Cantab.). British. 276, Milton Road, Cambridge. Scientific Information Officer. *Signed by :* A. H. Cooper, M. Oliver, T. Rendle.

Comrie, Allan McIntyre, B.Sc. (Glas.), A.R.I.C., M.P.S. British. 36, Dunard Street, Glasgow, N.W. Pharmacy Staff, Royal Technical College, Glasgow. *Signed by :* H. G. A. Anderson, W. A. Alexander, J. McLean.

***Cromartie, Ronald Ian Talbot.** British. Clare College, Cambridge. Student. *Signed by :* F. G. Mann, J. Harley Mason, P. Maitland, B. C. Saunders.

***Crawhill, John Currah,** B.Sc. (Lond.). British. 1, Gerard Road, Harrow. Research Chemist at National Institute of Medical Research. *Signed by :* C. R. Harington, D. F. Elliott, H. King.

Cundall, John Henry. British. 27, Albine Street, Moston, Manchester. Student at Royal Technical College, Stafford. *Signed by :* R. J. W. Reynolds, E. B. Robinson, D. M. Lever.

Davies, John Arthur Meirryn, B.Sc. (Wales). British. 8, Abbey Road, Port Talbot, Glamorgan. Assistant Master. *Signed by :* E. E. Ayling, C. W. Shoppee, R. H. Davies.

Davies, Rhys Glyn, M.Sc. (Wales). British. Penparc, Bryntirion Hill, Bridgend, Glamorgan. Assistant Research Superintendent. *Signed by :* C. B. Monk, J. B. Bowen, C. W. Davies.

Dawson, William, B.Sc. (Lond.), A.R.I.C. British. c/o Matheson, 32, Croftside Avenue, Glasgow, S.4. Research Student. *Signed by :* D. W. C. Ramsay, R. Stevenson, J. McLean.

Doull, Alexander Clark. British. 10, Alexander Drive, Alloa, Clackmannanshire. Head Brewer and Director, George Younger & Son, Ltd., Alloa. *Signed by :* I. M. Heilbron, E. N. Hamnett, A. H. Cook.

***Dunsmore, Helen Simpson,** B.Sc. (Glas.). British. 29b, The Esplanade, Greenock, Renfrewshire. Research Student. *Signed by :* J. C. Speakman, J. D. Loudon, J. C. James.

Dunsmuir, James Henry, B.Sc. (Lond.). British. "Carrigiea," Old Nassing Road, Broxbourne, Herts. Research Chemist at Allen and Hanburys Ltd., Ware. *Signed by :* N. R. Campbell, M. E. H. Fitzgerald, J. H. Hunt.

Edward, John Thomas, B.Sc. and Ph.D. (McGill), D.Phil. (Oxon.). Canadian. Chemistry Department, The University, Birmingham, 15. I.C.I. Research Fellow. *Signed by :* L. L. Bircumshaw, W. G. Overend, P. W. Kent.

***Ellerington, Trevor.** British. "Marville," Constable Road, Hornsea, E. Yorks. Assistant Analytical Chemist. *Signed by :* A. P. Backshell, G. R. Jenkinson, L. Balmforth.

***Evans, David Darwin,** B.Sc. (Wales), A.R.I.C. British. University College, Singleton Park, Swansea. Research Student. *Signed by :* R. H. Davies, E. E. Ayling, G. Roberts.

Ferrier, Richard, M.P.S. British. 24a, Portland Place, W. 1. Technical Adviser. *Signed by :* H. C. Happold, C. Kemplay, H. Lucas.

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Harpur, William Ware. British. 17, Chlorine Gardens, Malone Road, Belfast. Student at Queen's University. *Signed by :* H. Graham, C. L. Wilson, R. G. R. Bacon.

Herndon, Lyle Kermit, B.Ch.E. (Ohio State), M.S., Ph.D., and Ch.E. (W. Virginia). American. c/o Dr. G. D. Byrkit, Mathieson Chemical Corporation, Niagara Falls, N.Y. Director of Research. *Signed by :* H. M. Grotta, C. L. Wilson, F. D. Snell.

Heslop, James Alexander Barry, M.A. (Oxon.). British. 9, Glendale Avenue, Edgware, Middlesex. Student at Merton College, Oxford. *Signed by :* C. S. G. Phillips, D. H. James, F. M. Brewer.

Hookway, Harry Thurston, Ph.D. (Lond.), F.R.I.C. British. 28, Court Drive, Waddon, Croydon. Senior Scientific Officer, D.S.I.R. *Signed by :* G. A. H. Elton, C. L. Arcus, A. G. Davies.

***Horning, William Clarke,** B.A. (Toronto). Canadian. MacBrayne Hall, 11, Park Circus Place, Glasgow, C.3. Research Student at Glasgow University. *Signed by :* A. Rutherford, J. C. D. Brand, J. C. Speakman.

***Housley, John Rosindale.** British. 39, Sitwell Street, Spondon, Derby. Student at Nottingham University. *Signed by :* D. O. Jordan, C. C. Addison, B. D. Shaw.

Hughes, John Sylvan, B.Sc. (Lond.), F.R.I.C. British. 31, Victoria Park Road East, Cardiff. Chief Assistant Chemist to Public Analyst. *Signed by :* S. Dixon, H. B. Watson, J. Ormston.

Jackson, Graham George. British. 27, Knyvetan Road, Bournemouth. Student. *Signed by :* E. A. Seeley, A. S. Carlos, A. D. Bridge.

Jelfs, Ernest Charles Groves, B.Sc. (Lond.). British. 33, Springfield Avenue, Banbury, Oxon. Research Chemist at Esso Development Co., Abingdon. *Signed by :* E. B. Evans, J. D. Sandrock, A. M. Dominey.

***Jones, Maurice Harry,** B.Sc. (Lond.). British. 39, Elm Grove, Peckham, S.E. 15. Research Student at University College, London. *Signed by :* E. D. Hughes, D. A. Davenport, C. K. Ingold.

Jones, William Peter Robert, B.Sc. (Lond.). British. 10, Brooklyn Court, Loughton, Essex. Chemist. *Signed by :* F. Poppelsdorff, H. T. Young, P. Scott.

Landau, Manfred, B.Sc. (Witwatersrand). South African. 18, Elvetham Road, Edgbaston, Birmingham, 15. Research Chemist. *Signed by :* M. Gordon, C. E. Kendall, W. H. T. Davison.

***Large, Rowan Stanley.** British. Downs, Highways Hostel, Euxton, Nr. Chorley. With Chemical Inspectorate, Ministry of Supply. *Signed by :* T. P. Gervis, F. M. Bolton, A. E. Ross.

***Lawton, David.** British. Magdalen College, Oxford. Undergraduate. *Signed by :* L. E. Sutton, B. R. Brown, A. W. Birley.

***Lees, Peter,** B.Sc. (Dunelm.). British. 14, Fox and Hounds Road, Newcastle-on-Tyne, 5. Research Student. *Signed by :* G. R. Clemo, B. K. Davison, R. Raper.

Le Quesne, Walter John, M.A. (Oxon.). British. Jesus College, Oxford. Research Student. *Signed by :* W. A. Waters, R. J. Rallings, G. T. Young.

Lewis, Eric Albert. British. 32, Hollie Lucas Road, Kings Heath, Birmingham, 14. Chief Chemical Engineer. *Signed by :* L. L. Bircumshaw, B. M. Newman, F. M. Tayler.

***Little, James,** A.R.I.C. British. 77, Stevenson Street, Liverpool, 15. Research Chemist with I.C.I. *Signed by :* L. J. Burrage, A. G. Jones, H. K. Southern.

Lord, Frank. British. 37, Woodland Avenue, Hove, 4. Wholesale Chemist. *Signed by :* J. T. Setterington, J. R. Mansell, R. Goode.

***McFarlane, Neil,** B.Sc. (Glas.). British. c/o Webb, 6, Huncoat Avenue, Heaton Chapel, Stockport. Production Chemist at British Schering Ltd., Hazel Grove, Cheshire. *Signed by :* E. Booth, J. A. Beardall, E. N. Abrahart.

Mackenzie, Hector Douglas, B.Sc. (Birm.). British. 99, Holifast Road, Sutton Coldfield, Warwickshire. Research Student at Birmingham University. *Signed by :* L. L. Bircumshaw, J. C. Tatlow, L. F. Wiggins.

Mason, Harold, A.R.I.C. British. 12, Dymock Road, Preston. Senior Scientific Officer with Ministry of Supply. *Signed by :* J. R. Sanderson, F. M. Bolton, T. P. Gervis.

Merian, Rudolf Christian, Ph.D. (Basle). Swiss. 102, Irlam Road, Flixton, Nr. Manchester. Organic Chemist at the British Rayon Research Association. *Signed by :* D. I. McGilvray, J. L. Bolland J. Wilson.

***Meyer, Peter.** British. 1, Glenmore House, Richmond Hill, Richmond. Student at Bristol University. *Signed by :* F. H. Pollard, J. K. N. Jones, L. Hough.

***Milward, Gervaise Luigi,** B.A. (Oxon.). British. 11, Devas Road, Wimbledon, S.W. 20. Scientific Officer at the Chemical Research Laboratory, D.S.I.R., Teddington. *Signed by :* T. V. Arden, M. Corner, F. H. Burstall.

***Mummery, Francis Nigel Arnold.** British. 94, Stockton Lane, York. Student. *Signed by :* S. J. Fry, R. King, H. Fine.

Neill, Desmond William, M.Sc. (Lond.), A.R.I.C. British. 70, Marlborough Park South, Belfast. Secondary School Chemistry Master. *Signed by :* G. A. Dinsmore, F. Bell, I. F. B. Smyth.

Nurse, Ronald Walter Brown, M.Sc. (Lond.), F.Inst.P. British. Building Research Station, Bucknalls Lane, Garston, Watford. Principal Scientific Officer. *Signed by :* F. M. Lea, D. G. R. Bonnell, B. Butterworth.

***Pratt, Brenda Mary,** B.Sc. (Lond.), A.R.I.C. British. University College, University Road, Leicester. Assistant Lecturer. *Signed by :* L. Hunter, E. R. A. Peeling, F. R. Shaw.

***Pryde, Alan Millam,** A.R.I.C. British. 13, Viewforth Gardens, Edinburgh, 10. Research Student at Heriot-Watt College, Edinburgh. *Signed by :* H. B. Nisbet, R. G. M. Dakers, A. Mackie.

Richards, Geoffrey Norman, B.Sc. (Birm.). British. 65, Lawrence Lane, Old Hill, Staffs. Student. *Signed by :* L. L. Bircumshaw, L. F. Wiggins, D. A. Higgins.

***Richards, William Robert.** British. 362, Cardiff Road, Aberdare, Glamorgan. Student at Bristol University. *Signed by :* F. H. Pollard, J. K. N. Jones, L. Hough.

Roberts, Benjamin Joseph Hugh. British. 2, Cullen Street, Liverpool, 8. Analytical Chemist. *Signed by :* L. H. G. Green, W. T. Carter, N. A. Pryce.

Rollason, Ernest Clarence, M.Sc. and Ph.D. (Birm.). British. c/o Murex Welding Processes Ltd., Hertford Road, Waltham Cross. Research Manager. *Signed by :* W. Wardlaw, D. J. G. Ives, V. M. Ingram.

***Scott, James Anderson,** B.Sc. (Glas.). British. 60, Bellahouston Drive, Glasgow, S.W. 2. Research Student. *Signed by :* J. D. Loudon, J. C. Speakman, C. Buchanan.

***Sidlow, Richard,** A.R.I.C. British. 46, Stanley Gardens, Orrell Park, Liverpool, 9. Research Chemist. *Signed by :* S. Hill, C. Broomhead, G. P. C. Chambers.

Stephens, David, M.A. and B.Sc. (Oxon.) British. c/o 1, Young's Rise, Welwyn Garden City. Technical Officer at I.C.I. Plastics Division. *Signed by :* J. D. Burnett, J. W. C. Crawford, P. A. Small.

Suggate, Harold Gordon, B.Sc. (Lond.), A.R.I.C. British. 9, Ardleigh Green Road, Hornchurch. Senior Manufacturing Chemist at Ilford, Ltd. *Signed by :* J. D. Kendall, V. Gallafent, R. B. Collins.

***Tabor, Bryan Ernest.** British. 5, Argyle Road, North Harrow. Student. *Signed by :* H. T. S. Britton, R. King, S. J. Gregg.

Tauber, Harold, Dr.rer.nat. (Prague). Czech. 70, Netheravon Road, W. 4. Divisional Chemist, The Coca-Cola Co., London. *Signed by :* O. H. Gellner, L. H. Harris, G. Lewi.

***Thomas, Arthur Derrick.** British. 71, North Grove, Tottenham, N. 15. Student at Northern Polytechnic, N. 7. *Signed by :* W. Gerrard, W. A. Smeaton, A. B. Simmonds.

Thomson, Mrs. Christina Macgregor, B.Sc. (Glas.). British. c/o Paterson, 45, Clouston Street, Glasgow, N.W. Research Student at Glasgow University. *Signed by :* J. M. Robertson, T. H. Goodwin, J. C. Speakman.

Thomson, Samuel James, B.Sc. (Glas.). British. c/o Paterson, 45, Clouston Street, Glasgow, N.W. Assistant in Chemistry at Glasgow University. *Signed by :* J. Bell, T. H. Goodwin, J. M. Robertson.

Thornton, Max H., B.S. (Clemson Coll.), and Ph.D. (Purdue). American. Midwest Research Institute, 4049, Pennsylvania Avenue, Kansas City 2, Missouri. Chairman, Chemistry Research Division. *Signed by :* R. Adams, R. L. Evans, F. D. Snell.

Tughan, Victor Denis, B.Sc. (Q.U.B.). British. 18, Rosepark, Dundonald, Co. Down. Demonstrator at Queen's University, Belfast. *Signed by :* H. Graham, R. C. Pink, R. G. R. Bacon.

Turner, Leonard, B.Sc. (Lond.), A.R.I.C. British. 2b, Oxford Road, Moseley, Birmingham, 13. Research Student at Birmingham University. *Signed by :* C. R. Porter, D. H. Wiffin, R. Lang.

***Vosden, Denys John.** British. Station Road, Okehampton, Devon. Student at Oxford University. *Signed by :* W. A. Waters, J. C. Smith, F. M. Brewer.

Washbrook, Cyril Cecil, A.R.I.C. British. 51, Vancouver Road, Forest Hill, S.E. 23. Analyst and Experimental Officer, Chemical Inspectorate, Ministry of Supply. *Signed by :* D. F. Barke, M. Vahrman, P. A. Claret.

Westrop, Jack William, B.Sc. (Lond.). British. 2, Furnace Lane, Woodhouse Mill, Sheffield. Research at Sheffield University. *Signed by :* R. D. Haworth, E. G. Turner, C. J. Threlfall.

Williams, Henry, B.Sc. (Lond.). British. 15, Plaistow Grove, West Ham, E. 15. Lecturer at Sir John Cass College. *Signed by :* D. A. Andrews, D. W. Wilson, A. G. Lidstone.

Williams, Neville Ronald. British. 38, Rossall Avenue, Chapelfield, Radcliffe, Nr. Manchester. Assistant Research Chemist. *Signed by :* A. Burawoy, G. Baddeley, O. R. Howell.

Woods, George, B.Sc. (Manc.). British. 1, Whitemere Drive, Heaton Park, Manchester. Research Student at Manchester University. *Signed by :* H. B. Herbert, T. G. Halsall, T. N. Quibell.

Yost, John Franklin, B.S. (Western Maryland Coll.) and M.A. (Johns Hopkins). American. Brodbecks, Pennsylvania. Student at The Johns Hopkins University. *Signed by :* E. B. Reid, D. H. Andrews, W. A. Patrick.

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Bradlow, Herbert Leon, B.S. (Penn.), M.S. and Ph.D. (Kansas). American. Chemistry Department, University of California, Berkeley 4, California. Research Fellow. *Signed by :* D. S. Noyce.

Cadwell, Sidney Marsh, A.B. and Ph.D. (Chicago). American. United States Rubber Co., Research & Development Dept., General Laboratories, South & Market Streets, Passaic, New Jersey. Director. *Signed by :* F. D. Snell, W. A. Gibbons.

***DePuy, Charles Herbert,** B.S. (Calif.). American. Box 52, Department of Chemistry, Havemeyer Hall, Columbia University, New York 27. Student. *Signed by :* D. Y. Curtin.

Farber, Milton, B.S. (City College, N.Y.), A.M. and Ph.D. (Columbia). American. 1236, Virginia Avenue, New York 60, N.Y. Research Chemist. *Signed by :* W. Doering.

Graber, Robert Philip, Ph.D. (Wisconsin). American. 648, Westfield Avenue, Westfield, New Jersey. Research Chemist. *Signed by :* M. Tishler, C. R. Addinall.

Groszkinsky, Otto Ludwig, Dr.phil. (Heidelberg). German. 26, Deutsche Strasse, (21b), Dortmund-Eving, Germany, British Zone. Lecturer at Munster University, President of the Gesellschaft für Kohlentechnik m.b.H. *Signed by :* S. R. Carter.

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Hoff, Phillip Murray, jun., B.S. (Stanford Univ.). American. 1287E. Woodland Avenue, Chico, California. Student at Stanford University. *Signed by :* R. E. Swain.

Kade, Charles Frederick, jun., B.A. (Carleton Coll.), M.S. (North Dakota Agric. Coll.), Ph.D. (Illinois). American. Germantown Manor Apartments, Greene and Hortter Streets, Philadelphia 19, Pennsylvania. Director, Division of Medical Sciences, McNeil Laboratories, Inc. *Signed by :* M. G. Horning.

Mailboom, Charles Jose Richard, B.Sc. (Lond.), A.R.C.S., A.R.I.C. British. Administracion, Fabrica Urguaya de Alpargatas, Isidora Maria 1631, Montevideo, Uruguay. Chief Chemist. *Signed by :* H. J. T. Ellingham, R. L. Collett.

***Shairy, Muhammad Alawi.** British. Makerere College, Kampala, Uganda, East Africa. Student. *Signed by :* R. F. Naylor.

Tolbert, Bert Mills, B.S. and Ph.D. (Calif.). American. Radiation Laboratory, University of California, Berkeley 4, California. Research Chemist. *Signed by :* H. Hauptmann.

Van Meter, Clarence Taylor, Ph.D. (Pittsburgh). American. Reed & Carnrick, 155, Van Wagenen Avenue, Jersey City 6, New Jersey. Director of Research and Control at Reed & Carnrick. *Signed by :* F. D. Snell.

Wildi, Bernard Sylvester, Ph.D. (Ohio). American. Chemistry Department, Florida State University, Tallahassee, Florida. Assistant Professor of Chemistry. *Signed by :* W. L. Mosby.

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PAPERS RECEIVED.

(List of papers received between January 6th and February 9th, 1950.)

" Some compounds related to the aromatic nitrogen mustards." By GEORGE A. R. KON and JOHN J. ROBERTS.

" Steroids and related compounds. Part VIII. Some transformation products of 5-methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one." By M. DAVIS and V. PETROW.

" Germanium ferrocyanide." By M. PEISACH, W. PUGH, and F. SEBBA.

" The system $Al_2(SO_4)_3$–H_2SO_4–H_2O." By DUNCAN TAYLOR.

" Esters containing phosphorus. Part X. Radioactive diisopropyl fluorophosphonate." By B. C. SAUNDERS and T. S. WORTHY.

" The orientation of disubstituted fluoranthene derivatives." By NEIL CAMPBELL, W. W. EASTON, (MISS) J. L. RAYMENT, and (in part) J. F. K. WILSHIRE.

" Dinitrophenylhydrazones of the halogenobenzaldehydes." By O. L. BRADY and S. G. JARRETT.

" The replacement of the halogen group of acetohalogeno-sugars with retention of configuration." By G. A. HOWARD.

" Experiments on the synthesis of the pyrethrins. Part IV. Synthesis of cinerone, cinerolone, and cinerin-I." By LESLIE CROMBIE and STANLEY H. HARPER.

" The kinetics of the decomposition of nickel formate." By L. L. BIRCUMSHAW and JOSEPH EDWARDS.

" Syntheses of some derivatives of 4-aza- and of 2 : 4-diaza-fluoranthene." By J. W. COOK and J. S. MOFATT.

" A reversible indicator for use in titrations with potassium iodate." By R. BELCHER and S. J. CLARK.

" Polynuclear complexes of lanthanon sulphates." By R. C. VICKERY.

" The preparation of hexafluoroniobates, hexafluorotantalates, and hexafluorobismuthates by means of bromine trifluoride." By V. GUTMANN and H. J. EMELÉUS.

" The preparation of complex fluoro-acid salts of metals and of the nitronium ion by means of bromine trifluoride." By A. A. WOOLF and H. J. EMELÉUS.

" The preparation of nitrosyl complex fluorides and of fluorosulphonates by means of bromine trifluoride." By A. A. WOOLF.

" Synthesis of 2 : 3-dimethyl L-rhamnose; the action of sodium meta-periodate on 2 : 3- and 3 : 4-dimethyl L-rhamnoses." By F. BROWN, L. HOUGH, and J. K. N. JONES.

" The structure of *Sterculia setigera* gum. Part II. An investigation by the method of paper-partition chromatography of the products of hydrolysis of the methylated gum." By L. HOUGH and J. K. N. JONES.

" The structure of some diamines prepared by the Mannich reaction." By H. M. E. CARDWELL.

" Some reactions of thia*cyclo*hexan-4-one and 1-alkyl-4-piperidones." By H. M. E. CARDWELL.

" Hydrolysis products of *p*-bromobenzylthiuronium bromide." By H. M. E. CARDWELL.

" Oxidation of aldehydes in the gaseous phase. Part III. The inhibition of the oxidation of acetaldehyde by nitrogen peroxide." By C. A. MCDOWELL and J. H. THOMAS.

" The nucleic acids of normal and tumour tissues. The preparation and composition of a pentosenucleic acid from the fowl sarcoma G.R.C.H.15." By R. N. BEALE, R. J. C. HARRIS, and E. M. F. ROE.

" Quantitative studies of the reactivities of mixed carboxylic acid anhydrides. Part I. The composition of the acylation production in the reaction between acetic chloroacetic anhydride and primary aromatic amines." By A. R. EMERY and V. GOLD.

"Quantitative studies of the reactivities of mixed carboxylic acid anhydrides. Part II. The determination of some reaction velocities involving acetic chloroacetic anhydride." By A. R. EMERY and V. GOLD.

"Quantitative studies of the reactivities of mixed carboxylic acid anhydrides. Part III. The hydrolysis and some acylation reactions of a series of acetic chloroaliphatic acid anhydrides." By A. R. EMERY and V. GOLD.

"The reduction of *ortho*-quinones with lithium aluminium hydride." By J. BOOTH, E. BOYLAND, and E. E. TURNER.

"4-Aminosalicylic acid. Part II. The synthesis of 4-amino-2 : 5-dihydroxybenzoic acid and 4-amino-2 : 3-dihydroxybenzoic acid." By S. C. BHATTACHARYYA and D. E. SEYMOUR.

"Lanosterol. Part IX. Ketodihydrolanosterol." By M. J. BIRCHENOUGH and J. F. MCGHIE.

"Some halogeno-derivatives of 2 : 3-benzacridine." By BRIDGET CAIRNS and WILLIAM O. KERMACK.

"The reaction of poly(methyacrylamide) with hypohalite." By C. L. ARCUS.

"Structure and antimalarial activity. Part IV. Benziminazoles and thioldihydroglyoxalines." By A. T. JAMES and E. E. TURNER.

"Thermodynamic factors in stereo-specific processes. The transformation of the diastereoisomers of brucine 2'-(1-hydroxy*iso*propyl)diphenyl-2-carboxylate." By H. KACSER and A. R. UBBELOHDE.

"The reaction of fluorine with the oxides and oxy-compounds of manganese and rhenium." By E. E. AYNSLEY, R. D. PEACOCK, and P. L. ROBINSON.

"The synthesis of derivatives of 5 : 6-dihydroxyindole. Part II. 5 : 6-Dihydroxyindole and related compounds." By H. BURTON, (Miss) J. A. DUFFIELD, and P. F. G. PRAILL.

"Sn^{3+} in electron-transfer reactions." By R. C. VICKERY.

"A note on the Raman spectrum of the $AuCl_4$ ion." By J. D. S. GOULDEN, ALLAN MACCOLL, and D. J. MILLEN.

"*C*-Acetylation of α-β'-naphthindole derivatives." By S. G. P. PLANT and M. W. THOMPSON.

"A reversible indicator for use in oxidimetric titrations with standard sodium hydrochlorite." By R. BELCHER.

"A critical review of suggested values for the dissociation energy of fluorine." By M. G. EVANS, E. WARHURST, and E. WHITTLE.

"Strychnine and brucine. Part LI. Oxy*pseudo*strychnine." By C. A. FRIEDMANN.

"The constitution of xylan from Esparto grass (*Stipa tenacissima*, L.)." By S. K. CHANDA, E. L. HIRST, J. K. N. JONES, and E. G. V. PERCIVAL.

"Reactions of α-cyanoprene (1-cyanobuta-1 : 3-diene). Part III. Dimers." By (Mrs.) J. L. CHARLISH and W. H. DAVIES.

"Deoxy-sugars. Part XII. Experiments with the *O*- and the *N*-glycosides of some deoxy-sugars." By K. BUTLER, S. LALAND, W. G. OVEREND, and M. STACEY.

"The formation of osazones. Part I. The reaction of 2-hydroxy*cyclo*hexanone with aryl hydrazines." By G. J. BLOINK and K. H. PAUSACKER.

"Thermal cyclisation of *o*-aroyloxyacetoarones. A new synthesis of flavones." By (Miss) A. T. M. DUNNE, J. E. GOWAN, JOHN KEANE, B. M. O'KELLY, DENIS O'SULLIVAN, (Miss) M. M. ROCHE, P. M. RYAN, and T. S. WHEELER.

"Substituted anthracene derivatives. Part I. *cis*- and *trans*-9 : 10-Dimethyl-9 : 10-dihydroanthracene." By G. M. BADGER, (Miss) M. L. JONES, and R. S. PEARCE.

"Preparation of ethynylcarbinols from the bisulphite compounds of aldehydes and ketones." By J. CYMERMAN and K. J. WILKS.

"Pickeringite and the system $MgSO_4$–$Al_2(SO_4)_3$–H_2O." By HENRY BASSETT and WILLIAM WATT.

"The estimation of selenate and the preparation of some aluminium selenates." By HENRY BASSETT.

"The nucleic acid content of *Bact. lactis aerogenes*." By P. C. CALDWELL and SIR CYRIL HINSHELWOOD.

"Reactions of the alkylsulphate ion. Part I. Kinetics and mechanism of the reaction with hydroxide ion." By G. H. Green and J. Kenyon.

"Reactions of the alkylsulphate ion. Part II. Kinetics and mechanism of the reaction with phenoxide ion and the polar effects of substituents in the phenol nucleus." By G. H. Green and J. Kenyon.

"The bromination of allylbenzene." By M. Lora-Tamayo, F. Martin-Panizo, and R. Perez Ossorio.

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ERRATA.

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1945	774	14	For $q_1 = q/x(1 + bp)$ read $q_1 = q/(1 + bp)$.
	774	16 •	For $q_1 = q/44(1 + 0{\cdot}038p)$ read $q_1 = q/(1 + 0{\cdot}038p)$.
1946	748	43	*For* $C_{24}H_{36}O_2$ *read* $C_{28}H_{36}O_2$.
1949	711	1 •	For 4-*Keto*-1 : 1-*dimethylpiperidinium* read 4-*Keto*-1 : 1-*diethylpiperidinium*.
	1279	18 •	*Formula* (VI.) *should read* $[\overset{+}{N}HMe_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4{\cdot}\overset{+}{N}HMe_2]\bar{B}r_2$.
	1883	2 •	*For* nitroamines *read* nitroamides.
	2439	31 •	For 4-*phenyltetrahydrothiazine* read *tetrahydrothiazine*.
	2587	2 •	*For* 1-phenyl-1 : 2 : 3 : 4-tetrahydroisoquinone *read* 1-phenyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.
	2825	Table I	For *β-naphthyl-2-chloroethy'amine* read *N-β-naphthyl-N-methyl-N-2-chloroethylamine*.
	2998	35 •	*For* iodate *read* periodate.
1950	60	10	*Formula* (1) *should read* $\dfrac{f\phi(\mathbf{R}_{ss})H(E_j^{\circ})\phi(\mathbf{R}_{\circ})d\tau}{E(\mathbf{R}_{ss}) - E(\mathbf{R}_{\circ})}$
	210	25	*For* 160° *read* 147°.

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Whitmore, one of three talented brothers, received his early education at Handsworth Grammar School from which he entered the Chemistry school of the University of Birmingham in 1942. Always a brilliant scholar, he duly graduated with first class Honours and was awarded a Teaching Scholarship in the Chemistry Department.

He engaged in research work under Dr. F. J. Llewellyn in the *X*-ray department, studying the single-crystal *X*-ray methods of determining the crystal structure of organic substances (explosives). With Llewellyn he published some of the work in the Journal (*J.*, 1947, 881).

On gaining his Ph.D. in 1946 he was appointed to an I.C.I. Fellowship which he held in the Department of Physics at Birmingham with the object of building up, with the unusual facilities available, a small group engaged in studying radiochemistry. In addition it was the object of his new group to look after general chemical problems of the Nuclear Physics laboratory and to provide a link with interested workers in the Chemistry Department. From the start, owing to his generous and helpful nature, this new venture was a marked success and in his researches Whitmore had already begun to make a name for himself. He was particularly interested in the chemical state of atoms newly formed by nuclear transformation, *e.g.*, in the cyclotron. He paid a good deal of attention to phosphorus 32, and showed that this element when made by the action of fast neutrons on the sulphur in sodium sulphide appears, when brought into aqueous solution, as a phosphate ion. Several papers on this work were in preparation for the press when he was killed.

His particular hobby was mountaineering and he was an enthusiastic, generous and able leader among Midland climbers. He had an unusual talent for amateur dramatics and in his undergraduate days was in great demand by the various University societies, particularly the University Chemical Society.

He was unmarried and leaves a widowed mother. Because of the long period of training necessary for such work, Whitmore's untimely end is a sad loss to radiochemistry and to Birmingham, and his place cannot easily be filled.

M. STACEY.

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88. *The Ultra-violet Absorption Spectra of* 2 : 2′-, 2 : 4′-, 4 : 4′-*Dihydroxydiphenylmethanes,* 2 : 2′-*Dihydroxy-*5 : 5′-*dimethyldiphenylmethane and its* 3-, 4-, *and* 5-*Ring Polymers, and of* 4 : 4′-*Dihydroxydiphenylethane.*

By R. F. HUNTER, R. A. MORTON, and (in part) A. T. CARPENTER.

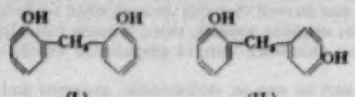
There is a small shift in maximum of ultra-violet light absorption towards the region of longer wave-length on passing from 2 : 2′- to 2 : 4′- and 4 : 4′-dihydroxydiphenylmethane, in agreement with similar difference for *o*- and *p*-substitution observed in the cresols and xylenols. The $-CH_2-$ link gives more satisfactory "insulation" between phenolic chromophores in 4 : 4′- than in 2 : 2′-dihydroxydiphenylmethane, and the insertion of a second $-CH_2-$ link, as in 4 : 4′-dihydroxydiphenylethane, further assists this. The appearance of a second band at 227 mμ. indicates, however, that even here "insulation" is not perfect. Substitution of methyl groups in the *p*-position to the hydroxyl groups in 2 : 2′-dihydroxydiphenylmethane slightly displaces the maximum to longer wave-length, and addition of a further cresol nucleus causes a smaller displacement on passing from the 2- to the 3-ring polymer of 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane; addition of further cresol nuclei, in the 4- and 5-ring polymers, has however no such effect. There is a steady increment of $\varepsilon_{max.}$ of approx. 3000 for each additional aromatic ring. A solution of the "clathrate" complex of the 4-ring polymer and ethylene dichloride gives the same absorption curve as the 4-ring polymer, indicating that the origin of the complex cannot be attributed to any form of enhanced dipole association.

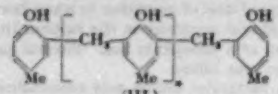
WITH the exception of the paper of de Boer, Houwink, and Custers (*Rec. Trav. chim.*, 1933, **52**, 710) and the later investigation of Mayer-Pitsch and Troger (*Z. Electrochem.*, 1941, **47**, 60) little work has been published on the ultra-violet absorption spectra of resins of the phenol–formaldehyde type or their intermediate products. During an examination of the ultra-violet absorption of certain Novolak and oil-modified Novolak resins, attention was directed to the isomeric 2 : 2′- (I), 2 : 4′- (II), and 4 : 4′-dihydroxydiphenylmethanes and to 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane (III; $n = 0$) and the higher polymers of the last.

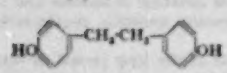
Preliminary measurements by the photographic method showed certain small and interesting differences which it was considered desirable to confirm with the Beckman spectrophotometer. The results obtained for (I), (II), (III; $n = 0$), and the 3-, 4-, and 5-ring polymers of (III), together with those for *o*- and *p*-cresol, *m*-4- and *m*-2-xylenol, and (IV) are given in the table. The detailed ultra-violet absorption curves for some of these compounds are shown in the figure.

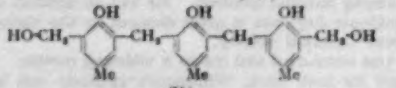
Compound.	$\lambda_{max.}$ (mμ.).	$\varepsilon_{max.}$	$\lambda_{min.}$ (mμ.).	$\varepsilon_{min.}$
o-Cresol	274	2,015	240	71·9
m-2-Xylenol	274	1,500	241	90
p-Cresol	280	1,995	244	70
m-4-Xylenol	280·5	2,148	245·7	98·2
2 : 2′-Dihydroxydiphenylmethane	275·5	5,110	242	262·5
2 : 4′-Dihydroxydiphenylmethane	277·5	4,490	248·5	462
4 : 4′-Dihydroxydiphenylmethane	280	3,795	250·5	444
(III; $n = 0$)	284	5,400	247·3	256
(III; $n = 1$)	288·5	8,480	248·3	450
(III; $n = 2$)	288	11,800	249	727
(III; $n = 3$)	288	14,725	249	1,250
4 : 4′-Dihydroxydiphenylethane	279	3,730	246	275
	227	17,625	—	—

It will be seen that there is a small shift of the maximum to the region of longer wave-length on passing from 2 : 2′- to 4 : 4′-dihydroxydiphenylmethane, the 2 : 4′-isomer occupying an









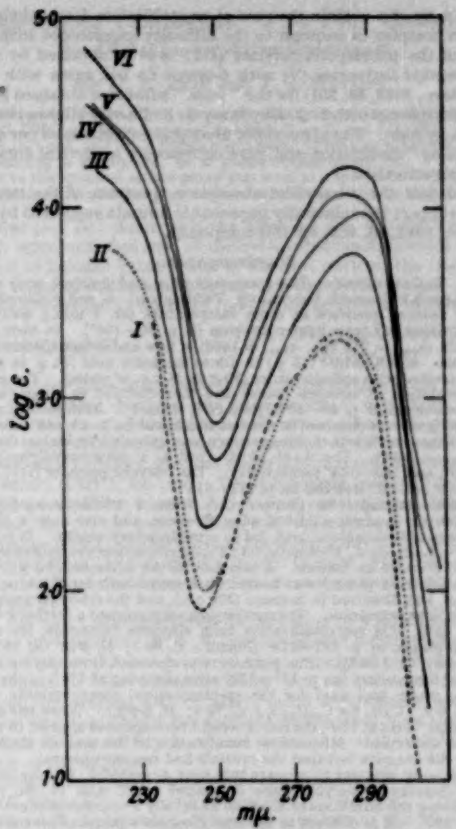
intermediate position in agreement with the similar differences for *o*- and *p*-methyl substitution in the cresols and xylenols. However, the substitution of a second methyl group in the xylenols has no effect on the wave-length of the absorption maxima of *o*- and *p*-cresol, although there is a curious and substantial drop in extinction coefficient in *m*-2-xylenol. This may perhaps be explained in terms of steric inhibition of resonance (cf. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890).

The $\varepsilon_{max.}$ and $\varepsilon_{min.}$ values for 2 : 2′-dihydroxydiphenylmethane, which are both greater than twice the respective values for *o*-cresol, show that the $-CH_2-$ link between the phenolic chromophores in the latter does not give perfect "insulation" (cf. Ramart-Lucas, *Bull. Soc. chim.*, 1932, **51**, 289). Comparison of $\varepsilon_{max.}$ and $\varepsilon_{min.}$ of 4 : 4′-dihydroxydiphenylmethane with those for *p*-cresol shows that more satisfactory "insulation" occurs in this isomer. The insertion of a second $-CH_2-$ link between the aromatic nuclei in 4 : 4′-dihydroxydiphenylethane (IV) confers still more satisfactory "insulation" of the chromophores (Ramart-Lucas, *loc. cit.*). The appearance of the band at 227 mμ., not shown by *p*-cresol, indicates, however, that even here "insulation" is not perfect (cf. Braude, *J.*, 1949, 1902).

Substitution of methyl in the *p*-position to the hydroxyl groups in 2 : 2′-dihydroxydiphenylmethane causes a slight displacement (7·5 mμ.) of the maximum towards the region of longer wave-length, and the addition of a further *p*-cresol nucleus causes a smaller displacement on passing from 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane (III; $n = 0$) to the tricyclic polymer (III; $n = 1$). The addition of further aromatic nuclei in the tetra- and penta-cyclic polymers (III; $n = 2$ and 3 respectively) is unaccompanied by any further displacement of the absorption maximum which remains at 288 mμ.

There is a steady increment in $\varepsilon_{max.}$ of approximately 3000 for each additional aromatic ring in passing from 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane to the 5-ring polymer, but the $\varepsilon_{max.}$ values for the cresols and *m*-4-xylenol are about 2000, indicating a roughly 50% increase in the probability of the relevant electronic transition. There is also an interesting rise in $\varepsilon_{min.}$ for each successive additional ring, indicating a steadily increasing probability for another transition with growth of the polymer chain.

	$\varepsilon_{max.}$	Diff.	$\varepsilon_{min.}$	Diff.
m-4-Xylenol	2,148	3252	98·2	157·8
(III; $n = 0$)	5,400	—	256	—
(III; $n = 1$)	8,480	3080	450	194
(III; $n = 2$)	11,800	3320	727	277
(III; $n = 3$)	14,725	2925	1250	523



I. p-*Cresol*. II. m-4-*Xylenol*. III. 2 : 2'-*Dihydroxy*-5 : 5'-*dimethyldiphenylmethane*.
IV. 3-*Ring polymer*. V. 4-*Ring polymer*. VI. 5-*Ring polymer*.

If the values for $\varepsilon_{max.}$ and $\varepsilon_{min.}$ are plotted against the number of aromatic nuclei, there is a good approach to linearity for the former and a less satisfactory one for the latter.

While the results therefore plainly show that the series is as a first-order problem simply additive, the second-order constitutive effects are by no means negligible.

In the course of attempts to purify the 4-ring polymer (III; $n = 2$) by recrystallisation from ethylene dichloride the formation was observed of an extraordinary stable crystalline 1 : 1-addition complex of this compound with the solvent which survived heating to 90° in a high vacuum (molecular distillation conditions). The ultra-violet absorption spectrum of a solution of the addition complex gave the same curve as the 4-ring polymer when molecular extinction coefficients were calculated on the basis of a 1 : 1 mol. ratio of the latter to ethylene dichloride: $\lambda_{max.}$, 288 mμ.; $\varepsilon_{max.}$, 9740; $\lambda_{min.}$, 249 mμ.; $\varepsilon_{min.}$, 572. The origin of the addition complex is therefore not attributable to any form of enhanced dipole association (cf. Hunter, Qureishy, and Samuel, *J.*, 1936, 1576) and it seems probable that this is a further example of the "clathrate" compounds described by Powell (*J.*, 1948, 61).

A molecular model of the 4-ring polymer based on accepted van der Waals radii showed that an ethylene dichloride molecule could be inserted under the more compact configuration of

the polymer. This may also explain the ease of crystallisation from ethylene dichloride in the form of the addition complex in contrast to the difficulty experienced with other solvents.

The properties of the pentacyclic polymer (III; $n = 3$) obtained by condensation of the tricyclic *bishydroxymethyl* derivative (V) with *p*-cresol do not agree with those described by Koebner (*Angew. Chem.*, 1933, **46**, 251) for the " pure " substance obtained by treating 4-methyl-2 : 6-bishydroxymethylphenol with 2 : 2'-dihydroxy-5 : 5'-dimethyldiphenylmethane ; no analysis was, however, given by him. The ultra-violet absorption spectrum of our specimen, which was purified by " molecular " distillation and gave satisfactory analytical data, therefore provides confirmation of its constitution.

It may be noted that the ultra-violet absorption spectrum of the tricyclic polymer (III; $n = 1$) also fails to support the inherently improbable formula suggested by Niederl and McCoy (*J. Amer. Chem. Soc.*, 1943, **65**, 629) for this compound.

Experimental.

Materials [*with* A. T. Carpenter].—The specimens of *o*- and *p*-cresol, *m*-4- and *m*-2-xylenol were obtained from the Chemical Research Laboratory, Teddington. *o*- and *p*-Cresol were further purified by distillation under reduced pressure at room temperature (*ca.* 1 mm.), and the *m*-2-xylenol was subjected to 5 recrystallisations from light petroleum (b. p. 80—100°). In view of the low extinction coefficient of the latter ($\lambda_{max.} = 272$ mμ; $\varepsilon_{max.} = 1460$), a new and larger specimen was prepared from *m*-2-xylidine as follows. *m*-2-Xylidine (15 g.) in dilute sulphuric acid (15 g. in 450 c.c. of water) was cooled and gradually treated with sodium nitrite (10 g. in 20 c.c. of water). The mixture was heated on a steam-bath until evolution of nitrogen ceased and then distilled in steam, and the distillate was extracted with light petroleum (b. p. 40—60°) [yield 60% (crude)]. After several recrystallisations from light petroleum, *m*-2-xylenol was obtained in needles which had m. p. 47—48° after prolonged drying in a vacuum. The extinction coefficient of this specimen was only slightly higher than that of the original ($\lambda_{max.} = 274$ mμ; $\varepsilon_{max.} = 1500$). The 2 : 2'-, 2 : 4'-, and 4 : 4'-dihydroxydiphenylmethane had m. p. 118—119·5°, 118—119°, and 162—163° respectively. The tricyclic polymer (III; $n = 1$) was prepared as described by Koebner (*loc. cit.*) and had m. p. 212—214°.

Tetracyclic Polymer.—Attempts to prepare this from 2 : 2'-dihydroxy-5 : 5'-dimethyldiphenylmethane and formaldehyde in acetic acid following Koebner, and also from a 10 : 1 mixture of these reactants in the presence of hydrochloric acid, led to unsatisfactory results. It was finally prepared by condensation of 2 : 2'-dihydroxy-5 : 5'-dimethyl-3 : 3'-bishydroxymethyldiphenylmethane (m. p. 146—147·5°) with excess of *p*-cresol as follows. A mixture of the dialcohol (10 g.), *p*-cresol (88 g.), and concentrated hydrochloric acid (8 c.c.) was heated on a water-bath for 2 hours, distilled in steam to remove excess of cresol, and dissolved in benzene (200 c.c.), and the crude polymer (9·7 g.; m. p. 172—178°) precipitated with light petroleum. The mother-liquors furnished a further 0·9 g. (m. p. 173—177°), the total yield being 65%. On recrystallisation from ethylene dichloride, the addition *complex* was obtained in hexagonal plates, m. p. 177—179° (Found : C, 69·7; H, 6·3; Cl, 13·2. $C_{31}H_{32}O_4,C_2H_4Cl_2$ requires C, 68·9; H, 6·3; Cl, 12·5%). The polymer was obtained from this by recrystallisation from benzene and heating of the product (m. p. 177—179° after sintering at 176°) in the " molecular " still at 170°. This specimen, which was used for the spectroscopical measurements, melted at 185—188° (Found : C, 80·2; H, 6·9. Calc. for $C_{31}H_{32}O_4$: C, 79·5; H, 6·8%). When the addition complex was heated in the " molecular " still at 170°, the loss in weight corresponded approx. to the loss of a molecular proportion of ethylene dichloride. Microscopic examination of the product showed that this had the same crystal habit as the complex but that the crystals had become opaque.

Pentacyclic Polymer.—An attempt to prepare this from 4-methyl-2 : 6-bishydroxymethylphenol and 2 : 2'-dihydroxy-5 : 5'-dimethyldiphenylmethane in glacial acetic acid in the presence of alcoholic hydrochloric acid following the directions of Koebner gave only a resinous product, which became brown but was unmelted at 260°. It is difficult to see how Koebner's preparation could lead to substantial amounts of the pentacyclic polymer since the proportions of reactants would be expected to give rise to a tricyclic derivative with a free active position available for further self-condensation. The pentacyclic polymer was finally prepared as follows. A mixture of the tricyclic bishydroxymethyl derivative (Zinke and Hanus, *Ber.*, 1941, **74**, 208) (5·25 g.), *p*-cresol (40 g.), and concentrated hydrochloric acid (5 c.c.) was heated on a water-bath for 2 hours (whereafter absence of free *o*-hydroxymethyl groups was inferred from the ferric chloride test), and excess of cresol removed by distillation in steam. The white amorphous material thus obtained was dissolved in benzene and precipitated with light petroleum. The product (6·5 g.) could not be crystallised from the usual solvents and was therefore purified by molecular distillation, after being subjected to preliminary degassing at 110°. The pentacyclic *polymer* distilled at 170—190°, furnishing a substance which sintered at 94—104° and melted at 112° [Found : C, 79·2; H, 6·7; *M* (Rast), 564, 569. $C_{39}H_{40}O_5$ requires : C, 79·6; H, 6·8; *M*, 588].

The 4 : 4'-dihydroxydiphenylethane was prepared by Clemmensen reduction of anisoin and subsequent demethylation (Richardson and Reid, *J. Amer. Chem. Soc.*, 1940, **72**, 413) and had m. p. 198—199°.

Spectroscopic Measurements.—The spectroscopic determinations were carried out on ethyl-alcoholic solutions of the compounds. The absorption curves were first plotted from measurements made by the photographic technique, using an iron–nickel arc and a sector photometer. All the quantitative determinations of maxima and minima were checked using fresh solutions on the Beckman photo-electric instrument with 1-cm. layers of alcoholic solution.

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Research and Development Department,
Bakelite Ltd., Tyseley, Birmingham, 11.
University of Liverpool.

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89. *Antituberculous Compounds. Part IV. Compounds related to Diethyl-ω-aryloxyalkylamines.*

By D. A. Peak and T. I. Watkins.

A series of compounds related to the active diethyl-ω-aryloxyalkylamines (I; X = O) (Part I; *J.*, 1949, 2880) has been prepared in which X = S, SO, SO_2, NH, NAlkyl, CO, CH_2, CO·O, or O·CO, n = 1 or 2, and Ar = trihalogenophenyl, phenyl, or naphthyl. In addition, the effect of interpolating a phenylene- or a phenyleneoxy-group [*cf.* V; X = C_6H_4(-*p*) or O-C_6H_4(-*p*)] next to the terminal amino-group was tried in a few cases. Although high *in vitro* activities were obtained in certain cases, no *in vivo* activity could be demonstrated.

Part I of this series (*loc. cit.*) dealt with the effect on the activity against *Mycobacterium tuberculosis* of such structural features of diethyl-ω-aryloxyalkylamines (I; X = O) as the number and position of halogen substituents in the aryl nucleus, the chain length *n*, and the replacement of the terminal diethylamino-group by other basic groups. As no evidence was available about the contribution of the ether linkage to the activity of these compounds, it was

(I.) Ar·X·$[CH_2]_n$·NEt_2 $\qquad$ C_6H_5·CO·CH(·CH_2·CH_2·CO·C_6H_5)·CH_2·NEt_2,HCl (II.)

though of interest to investigate compounds in which the oxygen atom was replaced by other atoms or groups. This paper describes the preparation of a number of such compounds. Wherever practicable, compounds halogenated in the aryl nucleus were prepared since, although such substitution in the aryloxy-series generally resulted in an increased activity only in the absence of serum, two cases had been observed where this increased activity had been maintained in the presence of serum (Part I, *loc. cit.*). The compounds prepared are listed in the accompanying table, together with the results of biological tests, further details of which will be published elsewhere. In the following discussion the numbers in parentheses following the names of compounds refer to the numbers of the compounds in the table. For convenience, compounds are referred to as the free bases although in most cases they were isolated as their water-soluble hydrochlorides or as Reineckates which were converted into aqueous solutions of the hydrochlorides for test.

As a first step, the effect of replacing the oxygen atom by a sulphur atom, or a sulphinyl or sulphonyl group was investigated. 2 : 4 : 6-Trichlorophenyl 2-diethylaminoethyl sulphide (1), sulphoxide (2), and sulphone (3) were prepared by conventional methods from the *sodium* salt 2 : 4 : 6-trichlorothiophenol. The sulphone could not be prepared from 2 : 4 : 6-*trichlorobenzenesulphinic acid*, the sodium salt of which failed to condense with diethylaminoethyl chloride. It will be seen that, while the sulphide corresponds very closely in activity to its oxygen analogue (Part I), the activity is reduced in the case of the sulphoxide and is of a very low order in the case of the sulphone.

Nitrogen analogues were prepared by the direct chlorination of *N*-2-diethylaminoethylanilines (I; n = 2, X = NR where R = H or alkyl) in acetic acid solution. This led to the formation of trichloro-derivatives (5, 7, 10) when the group attached to the nitrogen atom was small (R = H, Me, and CH_2·CH_2·NEt_2). With a larger alkyl group attached to the nitrogen, as in the case of the *N*-octyl and N-*cetyl* (12) compounds, dichloro-derivatives (11, 13) were produced, accompanied by considerable quantities of non-basic tars, presumably formed by fission of the side-chain. Three of these compounds (5, 7, 11) showed high activity in the absence of serum. In the only case (compound 5) where the activity was maintained sufficiently in the presence of serum to justify an *in vivo* test, no effect could be observed on the course of experimental tuberculosis in guinea pigs. Direct iodination and thiocyanation of *N*-methyl-*N*-2-diethylaminoethylaniline afforded *p*-iodo-*N*-methyl-*N*-2-diethylaminoethylaniline (8) and the *p*-thiocyanato-analogue (9) respectively, neither of which showed increased activity in comparison with the parent compound. *N*-2′-Diethylaminoethyl-1- and -2-naphthylamines (14, 15) showed low activity. In these cases direct chlorination led to extensive decomposition, and chloro-derivatives could not be prepared by this method. The orientation of the halogen atoms and the thiocyanato-group in all the foregoing compounds was not proved but the assigned positions were inferred by analogy with the behaviour of simple derivatives of aniline.

Diethyl-2-benzoylethylamine (16) showed a reduced activity in comparison with the oxygen analogue, diethyl-2-phenoxyethylamine (Part I). This compound (16) was prepared by the Mannich condensation of acetophenone with paraformaldehyde and diethylammonium chloride according to the method of Blicke and Burckhalter (*J. Amer. Chem. Soc.*, 1942, **64**, 451). The

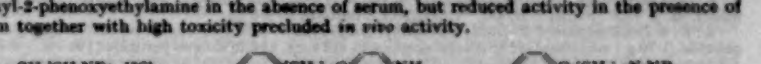
low yield in this reaction is ascribable, at least in part, to the simultaneous formation of major quantities of a *substance*, probably diethyl-2 : 4-dibenzoylbutylammonium chloride (II), resulting from the condensation of two molecules each of acetophenone and formaldehyde with one of

Compound.	Structure. (R = ·$(CH_2)_2$·NEt_2.)	Activity.* In absence of serum.	In presence of 10% serum.
(1) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphide	2 : 4 : 6-$C_6H_2Cl_3$·S·R	100 (500)	10
(2) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphoxide	2 : 4 : 6-$C_6H_2Cl_3$·SO·R	50	—
(3) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphone	2 : 4 : 6-$C_6H_2Cl_3$·SO_2·R	5 (10)	—
(4) *N*-2-Diethylaminoethylaniline	C_6H_5·NHR	—	1
(5) 2 : 4 : 6-*Trichloro*-N-2′-*diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3$·NHR	100—500	50
(6) *N*-Methyl-*N*-2-diethylaminoethylaniline	C_6H_5·NMeR	10	1—5
(7) 2 : 4 : 6-*Trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3$·NMeR	500—1000 (5000)	10—50
(8) *p*-Iodo-*N*-methyl-*N*-2-diethylaminoethylaniline	*p*-I-C_6H_4·NMeR	10	—
(9) *p*-Thiocyanato-*N*-methyl-*N*-2-diethylaminoethylaniline	*p*-NCS-C_6H_4·NMeR	10	—
(10) 2 : 4 : 6-*Trichloro*-NN-*bis*-2′-*diethylaminoethylanilina*	2 : 4 : 6-$C_6H_2Cl_3$·NR_2	10	10
(11) 2 : 4-Dichloro-*N*-2′-diethylaminoethyl-*N*-octylaniline	2 : 4-$C_6H_2Cl_2$·N(C_8H_{17})·R	1000	10
(12) N-2-*Diethylaminoethyl*-N-*hexadecylanilina*	C_6H_5·N($C_{16}H_{33}$)·R	1—5	—
(13) 2 : 4-Dichloro-*N*-2′-diethylaminoethyl-*N*-hexadecylaniline	2 : 4-$C_6H_2Cl_2$·N($C_{16}H_{33}$)·R	5 (50)	—
(14) *N*-2′-Diethylaminoethyl-1-naphthylamine	α-$C_{10}H_7$·NHR	—	1 (10)
(15) *N*-2′-Diethylaminoethyl-2-naphthylamine	β-$C_{10}H_7$·NHR	—	10 (50)
(16) Diethyl-2-benzoylethylamine	C_6H_5·CO·R	5	—
(17) Diethyl-2-*m*-aminobenzoylethylamine	*m*-NH_2·C_6H_4·CO·R	1	<1
(18) Diethyl-3-phenylpropylamine	C_6H_5·CH_2R	50—100	10—50
(19) 2′-Diethylaminoethyl 2 : 4 : 6-trichlorobenzoate	2 : 4 : 6-$C_6H_2Cl_3$·CO·OR	1—5	—
(20) 2′-Diethylaminoethyl 2 : 3 : 5-tri-iodobenzoate	2 : 3 : 5-$C_6H_2I_3$·CO·OR	10	1
(21) 2 : 4 : 6-Trichlorophenyl diethylaminoacetate	2 : 4 : 6-$C_6H_2Cl_3$·O·CO·CH_2·NEt_2	10	5—10
(22) *Phenyl* p-*aminobenzyl ether*	C_6H_5·O·CH_2·C_6H_4·NH_2-*p*	—	1—5
(23) 1-*Phenoxy*-2-p-*aminophenoxyethane*	C_6H_5·O·CH_2·CH_2·O·C_6H_4·NH_2-*p*	50—500	10
(24) 1-*Phenoxy*-2-(p-*diethylaminophenoxy*)*ethane*	C_6H_5·O·CH_2·CH_2·O·C_6H_4·NEt_2-*p*	500	50—100
(25) 1-(2 : 4 : 6-*Trichlorophenoxy*)-2-p-*aminophenoxyethane*	2 : 4 : 6-$C_6H_2Cl_3$·O·CH_2·CH_2·O·C_6H_4·NH_2-*p*	—	—

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Figures in parentheses represent dilutions at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

diethylammonium chloride. Attempts to prepare the 2 : 4 : 6-trichloro-derivative of compound (16) by several methods failed. Thus, 1 : 3 : 5-trichloro-2-iodobenzene formed a normal Grignard compound but this failed to react with 2-diethylaminoethyl cyanide. 2 : 4 : 6-Trichlorophenyl cyanide did not react with methylmagnesium iodide, but 2 : 4 : 6-*trichloroacetophenone* was readily prepared from 2 : 4 : 6-trichlorobenzoyl chloride and dimethylcadmium. This acetophenone was devoid of ketonic properties and could not be induced to undergo the Mannich reaction with formaldehyde and diethylammonium chloride, presumably owing to the reduction of the cationoid properties of the carbonyl group by the chlorine atoms. Steric factors probably played little part in this inactivation, since 2 : 3 : 5-*trichloroacetophenone* displayed a similar inertness. Finally, diethyl-2-*m*-aminobenzoylethylamine (17) was prepared by a Mannich condensation of *m*-benzamidoacetophenone with paraformaldehyde and diethylammonium chloride and hydrolysis of the resulting diethyl-2-*m*-benzamidobenzoylethylamine. It was hoped that this compound would yield by chlorination diethyl-2-(2 : 4 : 6-trichloro-3-aminobenzoyl)ethylamine and thence by deamination the required diethyl-2-(2 : 4 : 6-trichlorobenzoyl)ethylamine. Chlorination, however, led to non-basic gums, indicating degradation of the side-chain.

Catalytic reduction of diethyl-2-benzoylethylamine furnished the methylene analogue, diethyl-3-phenylpropylamine (18). This showed increased activity in comparison with diethyl-2-phenoxyethylamine in the absence of serum, but reduced activity in the presence of serum together with high toxicity precluded *in vivo* activity.



(III.) (IV.) (V.)

Compounds were also prepared in which the oxygen atom of (I; X = O) was replaced by ester groups of the type (–CO·O–) and (–O·CO–). 2'-Diethylaminoethyl 2 : 4 : 6-trichlorobenzoate (19) and 2 : 3 : 5-tri-iodobenzoate (20) were prepared from 2-diethylaminoethanol and the corresponding acid chlorides. In the former case considerable quantities of a by-product were obtained, apparently identical with diethylvinylammonium chloride (III), obtained by Ladenburg (*Ber.*, 1882, **15**, 1148) by the action of hydrogen iodide on diethylaminoethanol and conversion of the product into the chloride. It is presumably formed here by the elimination of the elements of 2 : 4 : 6-trichlorobenzoic acid from the ester. 2 : 4 : 6-Trichlorophenyl diethylaminoacetate (21) was prepared by the condensation of 2 : 4 : 6-trichlorophenol and diethylaminoacetyl chloride hydrochloride. It could not be prepared from 2 : 4 : 6-*trichlorophenyl chloroacetate* which with diethylamine underwent rapid fission to give *diethylammonium* 2 : 4 : 6-*trichlorophenoxide*. None of the compounds (19, 20, 21) showed high activity.

Finally, in view of the activity of compounds of type (IV) (Barry, O'Rourke, and Twomey, *Nature*, 1947, **160**, 800), it was thought of interest to prepare a few compounds of the type [V; n = 1 or 2, R = H or Et, X = C_6H_4(-*p*) or O·C_6H_4(-*p*)]. *Phenyl* p-*aminobenzyl ether* (22), prepared from the corresponding nitro-compound by reduction with aluminium amalgam, was an unstable compound as shown by its ready hydrogenolysis by other reducing agents and the formation of phenol in cold solutions of its *hydrochloride*. Chloro-derivatives were therefore not prepared. 1-*Phenoxy*-2-p-*aminophenoxyethane* (23), prepared by the reduction of 1-phenoxy-2-*p*-nitrophenoxyethane (Ryan and Kenny, *Sci. Proc. Roy. Dublin Soc.*, 1924, **17**, 305), had high activity only in the absence of serum. Ethylation gave 1-*phenoxy*-2-(p-*diethylaminophenoxy*)-*ethane* (24), the high activity of which was less affected by serum. No *in vivo* activity could, however, be demonstrated. Although 1-phenoxy-2-*p*-aminophenoxyethane was of normal basic strength, 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*aminophenoxyethane* (24), prepared by similar methods, was, unexpectedly, a very weak base, the *hydrochloride* and *lactate* of which were extensively hydrolysed by water and activity determinations were not carried out.

Experimental.

2 : 4 : 6-*Trichlorobenzenesulphinic Acid*.—2 : 4 : 6-Trichloroaniline (5 g.) was added at 30° to a solution of sodium nitrite (1·8 g.) in concentrated sulphuric acid (100 c.c.). The solution was then cooled and crushed ice (150 g.) added in portions at 5—8°. A small quantity of tar was removed from the surface, and the clear red solution was saturated at 3—5° with sulphur dioxide. A paste of copper powder (45 g.) and water was then added and the mixture stirred for 3 hours, the temperature being raised to 40° towards the end. The product was isolated as the ferric salt by the method of Thomas (*J.*, 1909, **95**, 342) except that, to avoid separation of the insoluble sulphinic acid, the ferric chloride was added to the filtrate before the addition of the ammoniacal extract of the copper powder. The orange precipitate was filtered off, washed with ethanol to remove coloured impurities, and decomposed with dilute ammonia. Filtration, acidification, and extraction with ether gave 2 : 4 : 6-*trichlorobenzenesulphinic acid* as a colourless solid, m. p. 115° (Found : S, 13·6. $C_6H_3O_2Cl_3S$ requires S, 13·0%). Attempts to condense the sodium salt with diethylaminoethyl chloride in ethanol, methanol, or benzene failed, the sulphinic acid being recovered unchanged.

Sodium Salt of 2 : 4 : 6-*Trichlorothiophenol*.—2 : 4 : 6-Trichloroaniline (5 g.) was diazotised by the method of Hodgson and Mahadevan (*J.*, 1947, 173), the dry diazonium sulphate (8·5 g.) dissolved in ice-water (100 c.c.), and a solution of potassium xanthate (4·5 g.) in ice-water (100 c.c.) added. The yellow, turbid solution was allowed to attain room temperature slowly overnight. (It was found that, if the mixture was allowed to reach room temperature immediately, the temperature rose and a violent reaction occurred.) The heavy brown oil (4·9 g.) was isolated with ether and refluxed for 45 minutes under nitrogen with a solution of potassium hydroxide (0·8 g.) in ethanol (50 c.c.). The solution was then evaporated *in vacuo* and the brown residue dissolved in water and shaken with ether to remove disulphide. The aqueous layer was acidified with acetic acid and extracted with ether, and the ethereal extract washed with water and dried. Titration of the solution with concentrated ethanolic sodium ethoxide until alkaline to phenolphthalein afforded a precipitate of the *sodium* salt of 2 : 4 : 6-trichlorothiophenol, obtained as a colourless solid (1·9 g.) after filtration and washing with ether (Found : S, 13·55; Na, 9·8. $C_6H_2Cl_3SNa$ requires S, 13·5; Na, 9·7%).

2 : 4 : 6-*Trichlorophenyl* 2'-*Diethylaminoethyl Sulphide Hydrochloride*.—The above sodium salt (3·7 g.) was refluxed with diethylaminoethyl chloride (2·1 g.) in absolute ethanol (80 c.c.) under nitrogen for 30 minutes. The mixture was evaporated to dryness *in vacuo* and the residue extracted with ether.

The ethereal solution was extracted with dilute hydrochloric acid, and the crude base liberated with alkali and extracted into ether. Addition of ethereal hydrogen chloride to the dried solution afforded **2 : 4 : 6-*trichlorophenyl* 2′-*diethylaminoethyl sulphide hydrochloride*** (2·2 g.), long prisms (from ethanol–ether), m. p. 183° (Found : N, 4·0. $C_{12}H_{15}NCl_4S$ requires N, 4·0%).

2 : 4 : 6-*Trichlorophenyl* 2′-*Diethylaminoethyl Sulphoxide*.—The free base from the foregoing hydrochloride (1·78 g.) was dissolved in glacial acetic acid (10 c.c.), and hydrogen peroxide (100 vol. ; 0·6 c.c. ; 1·3 mols.) added gradually at 10—15°. The mixture was kept overnight at room temperature and then evaporated *in vacuo*. The crude sulphoxide, liberated with dilute aqueous ammonia, was extracted into ether. Addition of ethereal picric acid afforded the *picrate* (1·81 g.), flat yellow needles (from absolute ethanol), m. p. 140° (Found : C, 39·0 ; H, 3·4 ; N, 10·2. $C_{18}H_{18}O_9N_4Cl_3S$ requires C, 38·75 ; H, 3·4 ; N, 10·0%). For test the picrate was converted into the free base with lithium hydroxide and dissolved in an equivalent of dilute hydrochloric acid.

2 : 4 : 6-*Trichlorophenyl* 2′-*Diethylaminoethyl Sulphone Hydrochloride*.—The free base from the sulphide hydrochloride (3·0 g.) was dissolved in 50% acetic acid (10 c.c.), and a solution of potassium permanganate (2·2 g.) in 50% acetic acid (74 c.c.) added at 0—3° during 1 hour. After a further 30 minutes at 5°, the mixture was decolourised with sulphur dioxide and evaporated to dryness *in vacuo*. The crude sulphone, liberated with aqueous ammonia, was extracted with ether. Addition of ethereal picric acid afforded the *picrate* (2·1 g.), flat needles (from ethanol), m. p. 145° (Found : C, 38·1 ; H, 3·0 ; N, 10·0. $C_{18}H_{18}O_{10}N_4Cl_3S$ requires C, 37·6 ; H, 3·3 ; N, 9·8%). The free base, obtained from the picrate with lithium hydroxide, was neutralised with ethanolic hydrogen chloride. Evaporation afforded the *hydrochloride*, colourless needles (from ethanol–ether), m. p. 170° (Found : N, 3·8. $C_{12}H_{17}O_2NCl_4S$ requires N, 3·7%).

***N*-2-*Diethylaminoethylaniline* and *NN-Bis*-(2-*diethylaminoethyl*)*anilines*.**—Aniline (93 g.), diethylaminoethyl chloride hydrochloride (172 g.), and powdered anhydrous sodium carbonate (106 g.) were mixed and heated on the steam-bath for 8 hours by which time evolution of carbon dioxide had ceased. The mixture was diluted with water and made slightly alkaline to Titan-yellow with aqueous sodium hydroxide, and the oil separated, dried, and fractionated. After a forerun of aniline (18 g.), *N*-2-diethylaminoethylaniline (108 g. ; b. p. 110—114°/1·6 mm.) was collected (Dewar, *J.*, 1944, 622, gives b. p. 162—164°/25 mm.) and finally a third fraction, b. p. 115—155°/1·6 mm. (32 g.). Repeated fractionation of the last fraction through an 9" Vigreux column gave pure *N*-bis-(2-diethylaminoethyl)aniline (8·6 g.), b. p. 146—148°/1·2 mm. (Found : N, 14·3. Calc. for $C_{18}H_{33}N_3$: N, 14·4%) (Stahmann and Cope, *J. Amer. Chem. Soc.*, 1940, **62**, 2494, give b. p. 174—177°/6 mm.). The *dipicrate* crystallised from ethoxyethanol in yellow plates, m. p. 170—170·5° (Found : C, 48·3 ; H, 5·1 ; N, 16·9. $C_{30}H_{33}O_{14}N_9$ requires C, 48·1 ; H, 5·2 ; N, 16·8%).

2 : 4 : 6-*Trichloro*-N-2′-*diethylaminoethylaniline*.—Chlorine was passed into a mixture of *N*-2-diethylaminoethylaniline (10 g.) and glacial acetic acid (100 c.c.) at 20° until the gain in weight was 11·1 g. (= 3 mols. of chlorine). Water (200 c.c.) was added, and the solution neutralised with solid sodium carbonate and finally made alkaline to Titan-yellow with sodium hydroxide. The liberated oil was isolated with ether and distilled, the fraction of b. p. 145—150°/1·5 mm. (7·2 g.) being collected. The redistilled product (6·2 g. ; b. p. 157—158°/2·5 mm.) was converted into the *picrate*, which after repeated crystallisation from methanol (yellow rhomboidal plates) had m. p. 150—151° (6·4 g.) (Found : N, 13·6. $C_{18}H_{20}O_7N_4Cl_3$ requires N, 13·3%). Reconversion of the picrate into the free base gave **2 : 4 : 6-*trichloro*-N-2′-*diethylaminoethylaniline*** as a colourless liquid (2·72 g.), b. p. 150—152°/2 mm. (Found : N, 9·9. $C_{12}H_{17}N_2Cl_3$ requires N, 9·5%).

2 : 4 : 6-*Trichloro*-NN-*bis*-(2′-*diethylaminoethyl*)*aniline*.—*NN*-Bis-(2-diethylaminoethyl)aniline (3·0 g.), chlorinated similarly, gave much tar and a fraction (2·8 g.), b. p. 168—178°/2 mm. Purified through the *dipicrate*, yellow prisms (from ethoxyethanol), m. p. 206—207° after sintering at 204° (Found : N, 15·0. $C_{30}H_{31}O_{14}N_8Cl_3$ requires N, 14·8%), this afforded **2 : 4 : 6-*trichloro*-NN-*bis*-(2′-*diethylaminoethyl*)-*aniline*** as a colourless liquid (1·04 g.), b. p. 170°/1·6 mm. (Found : N, 11·0. $C_{16}H_{26}N_3Cl_3$ requires N, 10·65%).

2 : 4 : 6-*Trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline*.—*N*-Methyl-*N*-2-diethylaminoethylaniline, prepared by the method used for *N*-2-diethylaminoethylaniline, had b. p. 124—125°/3 mm. (Dewar, *loc. cit.*, gives b. p. 165—170°/20 mm.). This material (10 g.), chlorinated in acetic acid, afforded a fraction, b. p. 148—152°/2·5 mm. (11·6 g.). Purified through the *picrate* (4·7 g.), m. p. 149—150° after repeated crystallisation from methanol (rhomboidal plates) (Found : N, 13·4. $C_{19}H_{22}O_7N_4Cl_3$ requires N, 13·0%), this gave **2 : 4 : 6-*trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline*** as a colourless liquid (1·7 g.), b. p. 142°/1 mm. (Found : N, 9·3. $C_{13}H_{17}N_2Cl_3$ requires N, 9·05%).

p-*Iodo*-N-*methyl*-N-2′-*diethylaminoethylaniline Hydrochloride*.—*N*-Methyl-*N*-2′-diethylaminoethylaniline (32·2 g.) was dissolved in concentrated hydrochloric acid (1 l.), and an excess (115 g., 4·5 mols.) of iodine monochloride in concentrated hydrochloric acid (300 c.c.) added. An oil separated which gradually formed greenish-yellow crystals when kept. The product (76 g.) was a complex of the desired compound with iodine monochloride. It dissolved readily in acetone (500 c.c.), the solution rapidly depositing a greyish-white solid (42 g.). The mother-liquor became dark and lachrymatory, probably owing to the formation of iodoacetone. Crystallisation from methanol–acetone afforded needles of **p-*iodo*-N-*methyl*-N-2′-*diethylaminoethylaniline hydrochloride*** (24 g.) in a solvated form, m. p. 135—140° (decomp.). When heated at 100° for some hours this lost 15% by weight and then crystallised from acetone in prisms, m. p. 168—169° (Found : C, 42·9 ; H, 6·0 ; N, 3·0. $C_{13}H_{21}N_2ClI$ requires C, 42·3 ; H, 6·0 ; N, 7·6%). Neither form could be converted into the other by seeding. They both afforded the same picrate, red needles m. p. 141—142°. Reconversion of the picrate into the hydrochloride *via* the free base afforded the solvated form irrespective of the origin of the picrate.

p-*Thiocyanato*-N-*methyl*-N-2′-*diethylaminoethylaniline Hydrochloride*.—To *N*-methyl-*N*-2′-diethylaminoethylaniline (5·1 g.) in carbon tetrachloride (10 c.c.) was added a solution of thiocyanogen in carbon tetrachloride (1·1 mols. ; Wood and Fiesser, *J. Amer. Chem. Soc.*, 1941, **63**, 2327). The solution became warm and the red oil which separated soon solidified. Recrystallisation from ethanol and aqueous methanol afforded the water-insoluble **p-*thiocyanato*-N-2′-*diethylaminoethylaniline monothiocyanate*** as

almost colourless needles, m. p. 95—96° (Found: N, 17·4. $C_{11}H_{20}N_2S_2$ requires N, 17·4%). The *picrate* separated from methanol in red needles, m. p. 125° (Found: N, 17·2. $C_{23}H_{24}O_7N_5S$ requires N, 17·2%). The free base was obtained by dissolving the crude thiocyanate (4·7 g.) in warm ethanol, adding an excess of 5*N*-hydrochloric acid, followed by an excess of dilute aqueous sodium carbonate, and isolating the resulting oil (2·8 g.) with ether. The *hydrochloride* separated from ethanol–ether in compact prisms (1·7 g.), m. p. 147—147·5° (Found: N, 14·1. $C_{11}H_{20}N_2ClS$ requires N, 14·0%).

2 : 4-*Dichloro*-N-2′-*diethylaminoethyl*-N-*octylanilins*.—*N*-2-Diethylaminoethylaniline (20 g.), octyl bromide (20 g.), and anhydrous potassium carbonate (20 g.) were heated at 150—160° for 7 hours. Water was then added, and the mixture made strongly alkaline to Titan-yellow and extracted with ether. The aqueous layer and a dark interface layer of quaternary hydroxide were discarded and the ether layer was concentrated. The residue afforded on distillation *N*-2′-diethylaminoethyl-*N*-octylaniline as a colourless oil (16·25 g.), b. p. 175—190°/2 mm. It was characterised as its *dipicrate*, yellow prisms (from methanol or ether), m. p. 82—83° (Found: N, 14·9. $C_{30}H_{40}O_{14}N_8$ requires N, 14·7%). Chlorination in acetic acid gave much tar and a fraction (8·1 g.), b. p. 188—195°/1·8 mm. Conversion into the Reineckate and repeated crystallisation from methanol afforded 2 : 4-*dichloro*-N-2′-*diethylaminoethyl*-N-*octylanilins Reineckate* as red plates, m. p. 140—142° (Found: C, 42·1; H, 5·85; N, 15·8; Cl, 11·1. $C_{24}H_{41}N_8Cl_2S_4Cr$ requires C, 41·5; H, 5·9; N, 16·2; Cl, 10·3%). The substance therefore probably contained some trichlorinated material. For test the Reineckate was converted into the hydrochloride with silver chloride in methanol, the methanol removed *in vacuo*, and the residue dissolved in water.

2 : 4-*Dichloro*-N-2′-*diethylaminoethyl*-N-*hexadecylaniline*.—In the same way N-2-*diethylaminoethyl*-N-*hexadecylaniline* was obtained in 50·5% yield as a colourless liquid, b. p. 235—244°/1·8 mm. and b. p. 239—242°/1·8 mm. on redistillation (Found: N, 6·9. $C_{32}H_{58}N_2$ requires N, 6·7%). Its *Reineckate* crystallised from methanol in red prisms, m. p. 135—136° (Found: N, 15·2. $C_{32}H_{59}N_8S_4Cr$ requires N, 15·2%). Chlorination of this material (20·8 g.) and fractionation of the product gave the dichloro-derivative as a colourless oil (9·6 g.), b. p. 246—250°/0·8 mm. It was purified as the *Reineckate*, red plates (from methanol), m. p. 131—132° (Found: C, 48·0; H, 7·2; N, 13·6; Cl, 8·4. $C_{32}H_{57}N_8Cl_2S_4Cr$ requires C, 47·8; H, 7·1; N, 13·9; Cl, 8·8%), and converted as above into the hydrochloride for testing.

N-2′-*Diethylaminoethyl*-1- and -2-*naphthylamines*.—Condensation of 1-naphthylamine (72 g.) and diethylaminoethyl chloride hydrochloride (86 g.) in the usual way afforded *N*-2′-diethylaminoethyl-1-naphthylamine as a colourless liquid (60·7 g.), b. p. 160—162°/0·8 mm. (Stahmann and Cope, *loc. cit.*, record b. p. 156—157°/1 mm.). Its *dipicrate* crystallised from ethanol in red prisms, m. p. 164—165° (Found: N, 16·3. $C_{32}H_{32}O_{14}N_8$ requires N, 16·0%). Its *dihydrochloride* separated from chloroform in tacky crystals, m. p. <100°, probably containing chloroform of crystallisation. Trituration with hot acetone yielded colourless crystals, m. p. 153—160° (Found: N, 9·2. $C_{16}H_{24}N_2Cl_2$ requires N, 8·9%). It gave a solution of low pH which could be adjusted to pH 5 without precipitation of the base. *N*-2′-Diethylaminoethyl-2-naphthylamine was prepared in similar yield as a colourless liquid with a strong blue fluorescence, b. p. 195°/3·5 mm. Its *monopicrate* separated from ethanol or acetic acid in yellow prisms, m. p. 152—153° (Found: N, 14·7. $C_{22}H_{23}O_7N_5$ requires N, 14·8%). For test the picrate was reconverted into the free base and dissolved in one equivalent of *N*-sulphuric acid. Attempted chlorination of both of these bases led to extensive decomposition and tar formation.

Diethyl-2-benzoylethylammonium Chloride.—Following the directions of Blicke and Burckhalter (*loc. cit.*), acetophenone (12 g.), diethylammonium chloride (11 g.), and paraformaldehyde (3·6 g.) were heated under reflux in absolute ethanol (20 c.c.) for 3 hours. The solution was filtered, the ethanol removed *in vacuo*, and the residue dissolved in water (50 c.c.). The free base was isolated by basification and extraction with ether. The ethereal solution was evaporated *in vacuo* and the residual oil kept over sulphuric acid *in vacuo* for 2 days to remove traces of diethylamine. (Failure to do this gave a low-melting final product very difficult to purify.) The oil was redissolved in ether, and the solution saturated with dry hydrogen chloride. The precipitated hydrochloride crystallised from acetone in needles (8·25 g.), m. p. 112—113° (Found: N, 5·85. Calc. for $C_{13}H_{20}ONCl$: N, 5·8%) (Blicke and Burckhalter, *loc. cit.*, give m. p. 108—110°).

In one experiment in which the aqueous solution was made just alkaline to Brilliant-yellow with aqueous sodium carbonate before extraction with ether, the aqueous layer subsequently deposited needles (7·6 g.), m. p. *ca.* 150°. Repeated crystallisation from methanol–ether and from water afforded a *substance*, probably diethyl-(2 : 4-dibenzoylbutyl)ammonium chloride, m. p. 193—194° after drying at 100° (Found: C, 70·5; H, 7·5; N, 3·8. $C_{23}H_{30}O_2NCl$ requires C, 70·6; H, 7·5; N, 3·75%).

Diethyl-3-phenylpropylammonium Chloride.—Diethyl-2-benzoylethylammonium chloride (9·6 g.) was hydrogenated with palladised charcoal (10%; 4 g.). Hydrogenation was rapid at 50°/atmospheric pressure, nearly the theoretical for 2 moles of hydrogen being absorbed. The catalyst was filtered off and the ethanol removed *in vacuo*. The residue, which partly crystallised, was triturated with acetone, and the crystals were separated. Crystallisation from acetone afforded diethyl-3-phenylpropyl-ammonium chloride as non-hygroscopic colourless plates (3·2 g.), m. p. 117—118° (Found: N, 6·3. Calc. for $C_{13}H_{22}NCl$: N, 6·15%) (Mannich and Chang, *Ber.*, 1933, **66**, *B*, 418, describe it as a hygroscopic substance, m. p. 119—120°). The free base had b. p. 118°/13 mm. (Found: N, 7·55. Calc. for $C_{13}H_{21}N$: N, 7·3%) (von Braun, *Ber.*, 1910, **43**, 3217, records b. p. 137—139°/22 mm.).

Attempted Reaction between 2 : 4 : 6-*Trichlorophenylmagnesium Bromide and* 2-*Diethylaminoethyl Cyanide*.—A Grignard solution was prepared from 1 : 3 : 5-trichloro-2-iodobenzene (3·05 g., 1 mol.; prepared by the method of Hodgson and Mahadevan, *loc. cit.*) and magnesium (0·42 g., 1½ mols.) in ether (50 c.c.), with ethyl bromide (0·5 g., ½ mol.) as entrainer. A solution of 2-diethylaminoethyl cyanide (2·1 g., 1½ mols.) was then added and the mixture refluxed for 30 minutes. After decomposition with ice and hydrochloric acid, the ethereal layer afforded 1 : 3 : 5-trichlorobenzene (2·2 g., 91%), m. p. 60° undepressed by admixture with authentic 1 : 3 : 5-trichlorobenzene, indicating at least 91% formation of trichlorophenylmagnesium iodide and practically no reaction of the latter with the diethylaminoethyl cyanide. The acid layer yielded only small quantities of basic ketonic material. Similar results were obtained when refluxing was continued for 24 hours or when the reaction was carried out in boiling

toluene or anisole. In the latter solvent some 2 : 2' : 4 : 4' : 6 : 6'-hexachlorodiphenyl, plates (from acetic acid), m. p. 112-5°, was isolated.

2 : 4 : 6- *and* 2 : 3 : 5-*Trichloroacetophenone.*—2 : 4 : 6-Trichlorophenyl cyanide (Meyer and Sudborough, *Ber.*, 1894, **27**, 3152) failed to react with methylmagnesium iodide in ether or anisole. Accordingly 2 : 4 : 6-trichlorobenzoyl chloride (11·5 g., 1 mol.) in benzene (50 c.c.) was added to a solution of dimethylcadmium (4 mols.) in benzene (prepared in the usual manner from methylmagnesium bromide and cadmium chloride). The mixture was heated under reflux for 3 hours and then decomposed with ice and hydrochloric acid, and the benzene layer washed with water, dried (Na_2SO_4), and concentrated. Fractionation of the residue afforded 2 : 4 : 6-*trichloroacetophenone* as a colourless liquid (6·8 g., 65%), b. p. 138—142°/7 mm., which quickly solidified and then had m. p. 60° (Found: C, 42·6; H, 2·6. $C_8H_5OCl_3$ requires C, 43·0; H, 2·2%). The substance did not form a 2 : 4-dinitrophenylhydrazone. Attempted condensation with dimethylammonium chloride and paraformaldehyde in acetic acid (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206), isoamyl alcohol (Kamp and Mossettig, *J. Amer. Chem. Soc.*, 1936, **58**, 1568), or nitrobenzene (Fry, *J. Org. Chem.*, 1945, **10**, 359) failed to yield any Mannich base, and 2 : 4 : 6-trichloroacetophenone was recovered unchanged. 2 : 3 : 5-Trichloroacetophenone, b. p. 120°/1 mm. (Found: C, 44·6; H, 2·8. $C_8H_5OCl_3$ requires C, 43·0; H, 2·3%), was prepared similarly in poor yield (20%), the major product being a *substance*, needles (from chloroform), m. p. 220° (Found: C, 41·6; H, 1·8%).

Diethyl-2-(m-*aminobenzoyl*)*ethylammonium Chloride.*—m-Aminoacetophenone (95·5 g.) and benzoic anhydride (160 g.) were heated at 100° for 20 minutes. The crude product was boiled with successive quantities of 3% aqueous sodium carbonate until the supernatant solution no longer gave a precipitate of benzoic acid on acidification. The residue was washed with water, dried, and crystallised from light petroleum (b. p. 80—100°), affording m-benzamidoacetophenone as needles, m. p. 108° (170 g.). This was stirred with diethylammonium chloride (85·7 g., 1·1 mols.), paraformaldehyde (32 g., 1·5 mols.), and concentrated hydrochloric acid (2 c.c.) in a mixture of benzene (300 c.c.) and nitrobenzene (300 c.c.) (cf. Fry, *loc. cit.*) and heated for 2 hours (oil-bath, 110—115°). A water-entrainer was now incorporated in the apparatus, the oil-bath heated to 145—150°, and water (29 c.c.) collected during 1 hour. The mixture on cooling deposited a thick crop of needles. Recrystallisation from absolute ethanol afforded *diethyl*-2-(m-*benzamidobenzoyl*)*ethylammonium chloride* (154·6 g.) as needles, m. p. 142° (Found: N, 7·6. $C_{20}H_{25}O_2N_2Cl$ requires N, 7·8%). Evaporation of the benzene–nitrobenzene mother-liquor and crystallisation of the residue from ethanol–ether gave a further crop (14·5 g.), m. p. 137—138°. The combined crops (169 g.) were heated under reflux for 6 hours with concentrated hydrochloric acid (1400 c.c.). The solution was cooled and the benzoic acid filtered off. The filtrate was extracted with ether and concentrated *in vacuo* to 150 c.c. On cooling, *diethyl*-2-(m-*aminobenzoyl*)*ethylammonium chloride* separated in needles (100·5 g.), m. p. 185° unaltered by further crystallisation (Found: N, 9·5. $C_{13}H_{21}ON_2Cl_2$ requires N, 9·5%). A further crop (19 g., m. p. 183—184°) was obtained by evaporation of the mother-liquor *in vacuo* to dryness and crystallisation of the residue from ethanol. Attempted chlorination of this product led in all cases to non-basic gums.

2-*Diethylaminoethyl* 2 : 4 : 6-*Trichlorobenzoate Hydrochloride.*—2 : 4 : 6-Trichlorobenzoyl chloride (3 g.) (Sudborough, *J.*, 1894, **65**, 1030; 1895, **67**, 602) was added to diethylaminoethanol (1·6 g.) in pure chloroform (8 c.c.) and, after 3 hours at room temperature, the mixture was warmed to 40° for 7 hours. Precipitation with ether and fractional crystallisation of the crystalline product from benzene–ethanol afforded two compounds. The first, m. p. 133—134·5° (Found: N, 10·3. Calc. for $C_4H_{11}NCl$: N, 10·3%), afforded an aurichloride, plates (from hot water), m. p. 138°. Ladenburg (*loc. cit.*) records no properties for diethylvinylammonium chloride but states that the aurichloride has m. p. 138—140°. The compound is therefore distinct from the normal polymerisation product of diethylaminoethyl chloride, tetraethylpiperazinium dichloride, which has the same empirical formula but does not melt below 300° and gives a diaurichloride of m. p. 236—237° (Slotta and Behnisch, *Annalen*, 1932, **497**, 170). The second compound was dissolved in water and then basified with aqueous sodium hydroxide, and the resultant oil isolated with ether. Reconversion into the hydrochloride gave 2-*diethylaminoethyl* 2 : 4 : 6-*trichlorobenzoate hydrochloride* (0·3 g.), needles (from ethanol–ether), m. p. 193° (Found: N, 4·15. $C_{13}H_{17}O_2NCl_4$ requires N, 3·9%).

2-*Diethylaminoethyl* 2 : 3 : 5-*Tri-iodobenzoate Hydrochloride.*—2 : 3 : 5-Tri-iodobenzoic acid (5·0 g.) (Wheeler and Johns, *Amer. Chem. J.*, 1910, **43**, 407) was refluxed with thionyl chloride (3 c.c.) and benzene (15 c.c.) until a clear solution was obtained. The benzene and excess of thionyl chloride were evaporated *in vacuo*, the yellow crystalline residue was dissolved in pure chloroform (15 c.c.), and 2-diethylaminoethanol (1·3 g., 10% excess) added. Cooling overnight in the ice-chest gave 2-*diethylaminoethyl* 2 : 3 : 5-*tri-iodobenzoate hydrochloride* as a pale yellow solid (4·2 g.), m. p. *ca.* 180° after softening at 165°. Recrystallisation from chloroform–acetone and finally from ethanol gave the substance as colourless prisms (2·35 g.), m. p. 184—185° (Found: N, 2·4. $C_{13}H_{17}O_2NCl_3I_3$ requires N, 2·2%).

2 : 4 : 6-*Trichlorophenyl Diethylaminoacetate Hydrochloride.*—(a) *Attempted preparation from* 2 : 4 : 6-*trichlorophenyl chloroacetate.* 2 : 4 : 6-Trichlorophenol (9·9 g.) was heated at 100° with excess of chloroacetyl chloride for 48 hours. Evolution of hydrogen chloride was slow and evidently incomplete. The mixture was poured into water and made faintly alkaline to Brilliant-yellow, and the solid filtered off. Recrystallisation from methanol gave 2 : 4 : 6-*trichlorophenyl chloroacetate* (3·8 g.), m. p. 69—70° unchanged by further crystallisation (Found: C, 34·6; H, 1·6. $C_8H_4O_2Cl_4$ requires C, 35·0; H, 1·5%). This substance (1·28 g.) was dissolved in dry ether (15 c.c.), and diethylamine (1·0 c.c.) added. Large prisms soon separated. The product (0·80 g.) recrystallised from ethanol in prisms, m. p. 157—159° (Found: N, 5·2. $C_{12}H_{15}ONCl_4$ requires N, 5·2%). It dissolved in dilute alkali to give free diethylamine and, on acidification, trichlorophenol. It was therefore *diethylammonium* 2 : 4 : 6-*trichlorophenoxide.*

(b) *From diethylaminoacetyl chloride and* 2 : 4 : 6-*trichlorophenol.* Chloroacetic acid (94·5 g., 1 mol.) was mixed with crushed ice, and diethylamine (219 g., 3 mols.) added portion-wise. The mixture was set aside at room temperature for 60 hours. It was then evaporated on the steam-bath after the addition of *hn*-sodium hydroxide (400 c.c., 2 mol.-equivs.) until the smell of diethylamine had disappeared. The solution was then made strongly acid to Congo-red and evaporated to a thick syrup. The syrup was

taken up in ethanol, filtered from sodium chloride, and again evaporated. The residue partly crystallised on storage in a desiccator over sulphuric acid. Oil was removed by trituration with methanol–acetone (1 : 4). The residue (61 g.) was extracted with methanol (50 c.c.) and filtered. Dilution of the filtrate with acetone (200 c.c.) gave *diethylaminoacetic acid hydrochloride* (32 g.) as large prisms, m. p. 125—126°. A further crop (7·0 g.; m. p. 125—126°) was obtained by re-extraction of the insoluble residue with methanol (15 c.c.) and precipitation with acetone (60 c.c.). The material so obtained was slightly hygroscopic. Recrystallisation from methanol–acetone gave non-hygroscopic material, m. p. 125—126° (Found: N, 9·35. $C_6H_{14}O_2NCl$ requires N, 9·35%).

The foregoing salt (3·0 g.) was finely ground, dried at 100°, and refluxed with thionyl chloride (2 c.c.) in dry chloroform (15 c.c.) until the solid just dissolved (20 minutes). Chloroform and excess of thionyl chloride were removed *in vacuo*, the residual light-brown solid redissolved in chloroform, and 2 : 4 : 6-trichlorophenol (2·5 g.) added. The solution was cooled in ice-water, and pyridine (2 c.c.) added dropwise. After 4 hours, the chloroform was removed *in vacuo*, and the residue dissolved in water (10 c.c.) and acidified to pH 2 with concentrated hydrochloric acid. Unchanged trichlorophenol was extracted with ether, the aqueous layer basified with solid sodium hydrogen carbonate to pH 8—9, and the resulting oil isolated with ether. After removal of the last traces of pyridine *in vacuo* over sulphuric acid, the residual dark-red mobile liquid was dissolved in ether, and a slight excess of ethanolic hydrogen chloride added. The resulting 2 : 4 : 6-*trichlorophenyl diethylaminoacetate hydrochloride* (3·3 g.) crystallised from acetone in colourless prisms, m. p. 148° (decomp.) (Found: N, 4·2. $C_{12}H_{15}O_2NCl_4$ requires N, 4·0%).

Phenyl p-Aminobenzyl Ether Hydrochloride.—Phenyl *p*-nitrobenzyl ether (4 g.; m. p. 94—95°) (Kumpf, *Annalen*, 1884, **224**, 104, gives m. p. 91°), dissolved in wet ether (80 c.c.), was reduced with amalgamated aluminium (4 g.), water (12 c.c.) being added portion-wise at such a rate as to maintain vigorous reaction. After 24 hours, the ether was filtered from the sludge of alumina, and the product precipitated as the hydrochloride by the addition of ethanolic hydrogen chloride (5 c.c. of 4·5*N*.). The crude product (4 g.) decomposed on attempted crystallisation from methanol, phenol being liberated. It was therefore shaken with ether and excess of dilute aqueous sodium hydroxide, the ether evaporated, and the residue (2·4 g.) crystallised from benzene–light petroleum. *Phenyl p-aminobenzyl ether* separated in needles (1·62 g.), m. p. 78—78·5° (Found: N, 7·2. $C_{13}H_{13}ON$ requires N, 7·0%). Precipitation of its ethereal solution with ethanolic hydrogen chloride gave the *hydrochloride* as a white powder, m. p. 140—145° (decomp.) (Found: N, 5·85. $C_{13}H_{14}ONCl$ requires N, 5·9%). It dissolved in water to give a slightly turbid solution which developed the smell of phenol when kept. Other methods of reduction of the nitro-compound, *e.g.*, neutral iron, stannous chloride, or ammoniacal ferrous sulphate, caused fission of the molecule.

1-*Phenoxy*-2-p-*aminophenoxyethane.*—1-Phenoxy-2-*p*-nitrophenoxyethane was prepared by the condensation of potassium *p*-nitrophenoxide (45 g.) and 2-phenoxyethyl bromide (50·2 g.) in boiling butanol (228 c.c.) for 40 hours. The reaction mixture was filtered hot. The product (53 g.) separated, on cooling, in needles, m. p. 87—88°. A sample recrystallised from ethanol to constant m. p. had m. p. 90° (Found: N, 5·4. Calc. for $C_{14}H_{13}O_4N$: N, 5·4%). Ryan and Kenny (*loc. cit.*) give m. p. 86°. The nitro-compound (53 g.) was heated under reflux for 24 hours with a solution of hydrated sodium sulphide (98·5 g.) and sulphur (13·1 g.) in 50% ethanol (103 c.c.). The solid which separated on cooling was filtered off, washed, and dissolved in warm benzene (400 c.c.). The benzene solution was washed first with water and then shaken with 5*N*-hydrochloric acid (100 c.c.), and the insoluble 1-*phenoxy*-2-p-*aminophenoxyethane hydrochloride* (46 g.; m. p. 206—208°) filtered off and washed with benzene. Recrystallisation from dilute hydrochloric acid gave the pure substance as needles, m. p. 210° (Found: N, 5·6. $C_{14}H_{14}O_2NCl$ requires N, 5·2%). The free *base* (39 g.) was obtained by warming the crude hydrochloride with a mixture of benzene (500 c.c.) and *N*-sodium carbonate solution (550 c.c.) until all went into solution, separating the benzene layer, and evaporating it *in vacuo*. A portion, crystallised twice from ethanol, had m. p. 109—110° (Found: N, 6·55. $C_{14}H_{13}O_2N$ requires N, 6·1%). The *hemipicrate* crystallised from benzene in yellow plates, m. p. 158° (Found: N, 10·2. $C_{34}H_{32}O_{11}N_8$ requires N, 10·2%).

1-*Phenoxy*-2-p-*diethylaminophenoxyethane.*—The foregoing base (5·25 g.) was heated and stirred under reflux with acetone (100 c.c.), ethyl iodide (4·1 c.c., 2·1 mols.), and potassium carbonate (6·4 g.) for 20 hours. The acetone was evaporated, water added to the residue, and the oil extracted with ether. The ethereal extract was filtered from flocculent, insoluble material, dried (Na_2SO_4), and evaporated. The residual oil (5·7 g.), which partly solidified when kept, was dissolved in a hot solution of picric acid (5·7 g.) in ethanol (100 c.c.). On cooling, 1-*phenoxy*-2-(p-*diethylaminophenoxy*)*ethane picrate* (8·25 g.) separated in yellow plates, m. p. 135—137° raised to 137—138° by recrystallisation (Found: C, 55·5; H, 5·5; N, 11·1. $C_{24}H_{26}O_9N_4$ requires C, 56·1; H, 5·1; N, 10·9%). This was shaken with aqueous lithium hydroxide and ether, and the ethereal solution separated and evaporated. The residual oil (4·3 g.), crystallised from methanol (10 c.c.) at 0°, furnished the free *base*, m. p. 40—41° (Found: N, 5·05. $C_{18}H_{23}O_2N$ requires N, 4·9%). For test the substance was dissolved in an equivalent of dilute hydrochloric acid to give a solution of pH 5.

1-(2 : 4 : 6-*Trichlorophenoxy*)-2-p-*aminophenoxyethane.*—2 : 4 : 6-Trichlorophenol (15 g.) was dissolved in ethanol (100 c.c.), and a solution of sodium hydroxide (3·1 g.) in water (10 c.c.) added. The solution was then heated under reflux with ethylene dibromide (30 g.) for 30 hours. The ethanol was evaporated *in vacuo*, and the crystalline residue isolated with ether and distilled. 2-(2 : 4 : 6-*Trichlorophenoxy*)*ethyl bromide* was obtained as a colourless liquid (15·4 g.), b. p. 184—185°/3 mm., which soon solidified. Crystallisation of a small portion from ethanol afforded long needles, m. p. 49—50° (Found: C, 31·6; H, 2·2. $C_8H_6OCl_3Br$ requires C, 31·5; H, 2·0%).

The foregoing compound (14·8 g.) was added to a suspension of sodium *p*-nitrophenoxide formed by adding sodium hydroxide (2·0 g.) in water (5 c.c.) to a solution of *p*-nitrophenol (6·8 g.) in ethanol (100 c.c.). The mixture was heated under reflux for 20 hours, only a part of the solid having by then dissolved. The ethanol was evaporated *in vacuo* and the residue extracted with benzene. The benzene extract was shaken with dilute sodium hydroxide and evaporated, the residue solidifying on cooling. Crystallisation from ethanol (50 c.c.) afforded crude 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*nitrophenoxyethane* (10·4 g.), m. p.

80—100°, contaminated with unchanged trichlorophenoxyethyl bromide. Recrystallisation of a small portion from methanol gave needles, m. p. 116—116·5° (Found: N, 4·4. $C_{16}H_{20}O_4NCl_3$ requires N, 3·9%). The crude product (8·5 g.) was reduced as previously with amalgamated aluminium (8·5 g.) in ether (340 c.c.), and ethanolic hydrogen chloride added to the ethereal filtrate. The precipitated crude hydrochloride was reconverted into the free base. Crystallisation from light petroleum–benzene gave 1-(2 : 4 : 6-*trichlorophenoxy*)-2-*p-aminophenoxyethane* (2·6 g.) as needles, m. p. 77—78° (Found: N, 4·3. $C_{14}H_{12}O_2NCl_3$ requires N, 4·2%). The *hydrochloride* crystallised from 2*N*-hydrochloric acid or methanol in rosettes of needles, m. p. 237—239° (Found: N, 3·7. $C_{14}H_{13}O_2NCl_4$ requires N, 3·8%). The *lactate* similarly crystallised from aqueous lactic acid in needles, m. p. 143—144° (Found: N, 3·5. $C_{17}H_{18}O_5NCl_3$ requires N, 3·2%).

Both salts were largely hydrolysed in solution, giving turbid solutions of pH 2 which deposited free base on cooling.

The authors gratefully acknowledge their indebtedness to Mr. C. E. Coulthard, Dr. L. Dickinson, and Miss B. Croshaw for biological tests, and to Dr. W. F. Short for his interest in the work. They also thank Miss M. Birchmore and Miss F. Skidmore for carrying out the analyses. One of the compounds (no. 8) was prepared during work carried out on behalf of the Therapeutic Research Corporation of Great Britain Ltd.

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD., NOTTINGHAM.

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90. *Antituberculous Compounds. Part V.* 2-*Sulphanilamido-5-alkyl*-1 : 3 : 4-*oxadiazoles and -thiadiazoles and Related* iso*Thiosemicarbazones and* iso*Thioureas.*

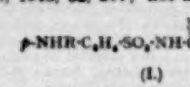
By J. D. BROOKS, P. T. CHARLTON, P. E. MACEY, D. A. PEAK, and W. F. SHORT.

Following the observation of the specific *in vitro* activity, against *Mycobacterium tuberculosis*, of 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole (I; X = O, R = H, R′ = Me), a number of derivatives and analogues of this compound have been prepared. These include N^4-acyl derivatives and higher alkyl homologues (R′ = amyl, undecyl, and heptadecyl). Similar activity is shown by corresponding thiadiazoles (I; X = S).

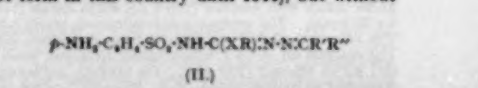
Structurally analogous *iso*thiosemicarbazones have also been prepared. Although these were generally active *in vitro*, a selected compound showed no activity *in vivo* in contrast to the closely related, therapeutically active benzaldehyde thiosemicarbazones (Domagk, *Nordisk Medicin*, 1948, **39**, 1322).

A series of *iso*thioureas has also been prepared. *N*-Aryl*iso*thioureas showed high *in vitro* activity only in the absence of serum. Cyclic *iso*thioureas, such as 2-aminobenzthiazoles and 2-alkylthiopyrimidines, were without interest.

THE work to be described in the present paper arose from the observation made in 1944 that 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole (I; X = O, R = H, R′ = Me), while virtually inactive against organisms normally sensitive to sulphonamides, exhibited a highly specific activity *in vitro* against *Mycobacterium tuberculosis*. The compound, first prepared in 1943, has since been described (Tappi and Migliardi, *Arch. Sci. Biol.*, 1941, **27**, 170; Tappi, *Rec. Trav. chim.*, 1943, **62**, 207; not available in abstract form in this country until 1944), but without



(I.) (a)



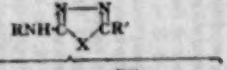
(II.)

reference to its antituberculous activity. Complete inhibition of the growth of *M. tuberculosis* occurs at dilutions of 1 in 10,000—50,000, 4-aminosalicylic acid showing the same activity under the same conditions of test. Although this activity is of a comparatively low order, the low toxicity of the compound and its apparent persistence in high concentrations in the blood-stream gave promise of chemotherapeutic activity. An extensive series of *in vivo* tests failed to indicate any such activity, and this inactivity was later accounted for by the demonstration that the Bratton–Marshall estimation of blood-levels is misleading in this case, the compound being in fact rapidly metabolised to an inactive substance. Details of this work will be published elsewhere.

Before the explanation of this negative result was obtained, derivatives and homologues had been prepared in order to elucidate the structural features of activity and in the hope of increasing the activity. The compounds prepared are summarised in Table I, together with their *in vitro* activities. In the subsequent discussion figures in parentheses following the name of a compound refer to the number of the compound in this or other tables.

TABLE I.

5-Amino-2-alkyl-1 : 3 : 4-oxadiazoles and -thiadiazoles.



Compound. -1 : 3 : 4-oxadiazole or -thiadiazole.	X.	R'.	R''.	M. p.	Formula.	Found N, %.	Req. N, %.	Activity * in absence of serum.
(1) 2-Sulphanilamido-5-methyl-	O	Me	$NH_2 \cdot C_6H_4 \cdot SO_2 \cdot$	176°	$C_9H_{10}O_3N_4S$	21·5	22·0	10—50
(2) 2-(3 : 5-*Di-iodosulphanilamido*)-5-*methyl-*	O	Me	$NH_2 \cdot C_6H_2I_2 \cdot SO_2 \cdot$	228—229	$C_9H_8O_3N_4I_2S$	11·3	11·1	1
(3) 2-N^a-Acetylsulphanilamido-5-methyl-	O	Me	$AcNH \cdot C_6H_4 \cdot SO_2 \cdot$	212	$C_{11}H_{12}O_4N_4S$	—	—	< 1
(4) 2-N^a-*Hexoylsulphanilamido-5-methyl-*	O	Me	$C_5H_{11} \cdot CO \cdot NH \cdot C_6H_4 \cdot SO_2 \cdot$	203	$C_{15}H_{20}O_4N_4S$	15·9	15·9	5
(5) 2-N^a-*Dodecoylsulphanilamido-5-methyl-*	O	Me	$C_{11}H_{23} \cdot CO \cdot NH \cdot C_6H_4 \cdot SO_2 \cdot$	124	$C_{21}H_{32}O_4N_4S$	12·7	12·8	5
(6) 2-N^a-*Stearoylsulphanilamido-5-methyl-*	O	Me	$C_{17}H_{35} \cdot CO \cdot NH \cdot C_6H_4 \cdot SO_2 \cdot$	128—129	$C_{25}H_{40}O_4N_4S$	10·7	10·8	1
(7) 2-*Toluene-p-sulphonamido-5-methyl-*	O	Me	$CH_3 \cdot C_6H_4 \cdot SO_2 \cdot$	152	$C_{16}H_{17}O_3N_3S$	16·7	16·6	1
(8) 2-*Amino-5-amyl-*	O	C_5H_{11}	H	151	$C_7H_{13}ON_3$	27·2	27·1	1
(9) 2-*Amino-5-undecyl-*	O	$C_{11}H_{23}$	H	150—151	$C_{13}H_{25}ON_3$	17·3	17·6	1
(10) 2-*Amino-5-heptadecyl-*	O	$C_{17}H_{35}$	H	143	$C_{19}H_{37}ON_3$	13·5, 13·3	13·0	< 1
(11) 2-N^a-*Acetylsulphanilamido-5-amyl-*	O	C_5H_{11}	$AcNH \cdot C_6H_4 \cdot SO_2 \cdot$	186	$C_{15}H_{20}O_4N_4S$	15·9	15·9	1
(12) 2-N^a-*Acetylsulphanilamido-5-amyl-*	S	C_5H_{11}	$AcNH \cdot C_6H_4 \cdot SO_2 \cdot$	201—202	$C_{15}H_{20}O_3N_4S_2$	15·2	15·2	1
(13) 2-*Sulphanilamido-5-amyl-*	O	C_5H_{11}	$NH_2 \cdot C_6H_4 \cdot SO_2 \cdot$	148—149	$C_{13}H_{18}O_3N_4S$	18·3	18·1	50
(14) 2-*Sulphanilamido-5-amyl-*	S	C_5H_{11}	$NH_2 \cdot C_6H_4 \cdot SO_2 \cdot$	182	$C_{13}H_{18}O_2N_4S_2$	17·4	17·2	50
(15) 2-*Sulphanilamido-5-undecyl-*	O	$C_{11}H_{23}$	$NH_2 \cdot C_6H_4 \cdot SO_2 \cdot$	105—107	$C_{19}H_{32}O_3N_4S$	14·1	14·2	100
(16) 2-*Sulphanilamido-5-heptadecyl-*	O	$C_{17}H_{35}$	$NH_2 \cdot C_6H_4 \cdot SO_2 \cdot$	91—93	$C_{25}H_{44}O_3N_4S$	11·4	11·7	10

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 6 weeks in modified Long's medium (by the floating-pellicle method). Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

(1) Preparation by Dr. H. Kitchen. Found: C, 42·55; H, 4·4. Calc. for $C_9H_{10}O_3N_4S$: C, 42·5; H, 4·0%. Tappi and Migliardi (*loc. cit.*) and Tappi (*loc. cit.*) record m. p. 172°. (3) Found: S, 10·6. Calc. for $C_{11}H_{12}O_4N_4S$: S, 10·8%. Tappi (*loc. cit.*) records m. p. 213°. (4), (5), (6), and (7) Preparations by Dr. R. P. Hullin. (8) Colourless needles by precipitation of its solution in hydrochloric acid with dilute ammonia solution.

2-N^4-*Hexoyl-*, *-dodecoyl-*, and *-stearoyl-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazoles* (4, 5, 6) were prepared by conventional methods from 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole. The activity was in all cases lower than that of the parent compound and the N^4-acetyl derivative (3) was completely inactive, indicating the necessity for a free N^4-amino-group. This was further shown by the low activity of *2-toluene-p-sulphonamido-5-methyl-1 : 3 : 4-oxadiazole* (7), prepared from 2-amino-5-methyl-1 : 3 : 4-oxadiazole (Stollé and Fehrenbach, *J. pr. Chem.*, 1929, **122**, 289; De, *J. Indian Chem. Soc.*, 1930, **7**, 651) and toluene-*p*-sulphonyl chloride. Iodination of the 2-sulphanilamido-compound with iodine monochloride afforded a *di-iodo*-derivative (2) of low activity, again possibly due to the weakened basicity of the N^4-amino-group.

The homologous series, *2-amino-5-amyl-*, *-undecyl-*, and *-heptadecyl-1 : 3 : 4-oxadiazoles* (8, 9, 10), was prepared from the corresponding 1-acylthiosemicarbazides by the action of lead monoxide in boiling ethanol (cf. Stollé and Fehrenbach, *loc. cit.*). The yields were progressively poorer in the case of the higher homologues, particularly the heptadecyl compound for which cyclisation was retarded by the formation of an insoluble lead salt of the 1-stearoylthiosemicarbazide. All three compounds were of low activity. Their *sulphanilyl* derivatives (13, 15, 16), prepared by conventional methods, showed activity which was of a high order in the case of the undecyl compound. No *in vivo* tests were carried out in view of the realisation at this time of the rapid inactivation of the methyl homologue in the blood-stream. One thiadiazole was prepared. 1-Hexoylthiosemicarbazide was cyclised with benzenesulphonic acid to *2-amino-5-amyl-1 : 3 : 4-thiadiazole* and thence converted into the N^4-*acetylsulphanilyl* and *sulphanilyl* derivatives (12, 14). The last-named showed the same activity as its oxygen analogue; its acetyl derivative exhibited the same weak activity as 2-N^4-*acetylsulphanilamido-5-amyl-1 : 3 : 4-oxadiazole* (11).

In view of the unfavourable *in vivo* properties of this series, modifications of the structure were sought. A possible line of approach appeared to be the preparation of uncyclised forms of the molecule in which fission may be regarded to have taken place at the bond (*a*) in (I). This would lead to 4-sulphanilyl-3-alkyl*iso*semicarbazones (II; X = O, R = alkyl, R′ and R″ = H or alkyl) from the oxadiazoles and to 4-sulphanilyl-3-alkyl*iso*thiosemicarbazones (II; X = S, R = alkyl, R′ and R″ = H or alkyl) from the thiadiazoles. *In vitro* tests with 2-sulphanilamido-5-methyl-1 : 3 : 4-thiadiazole (I; X = S, R = H, R′ = Me), a supply of which was kindly made available to us by the Therapeutic Research Corporation of Great Britain Ltd., had shown that it possessed activity similar to that of the oxadiazole and that it was subject to the same *in vivo* limitations. Results with the amyl homologues (12, 14) confirmed that oxygen and sulphur were interchangeable in the molecule. Since 3-alkyl*iso*thiosemicarbazones were more readily accessible than 3-alkyl*iso*semicarbazones, it was proposed to prepare a series of sulphanilyl derivatives of the former. The first compound prepared, acetone 3-ethyl*iso*-thiosemicarbazone (17; Table II) had, itself, fair activity but its 4-*sulphanilyl* derivative (18) was almost completely devoid of activity. Further work was therefore directed towards examination of the 3-alkyl*iso*thiosemicarbazones themselves. These were prepared smoothly in all cases by the method of Baird, Burns, and Wilson (*J.*, 1927, 2527) and their properties and activities are summarised in Table II. Benzaldehyde 3-ethyl*iso*thiosemicarbazone (19) was as active as the acetone analogue and, in a series of 3-alkyl homologues, high activity was reached with the butyl derivative (20), falling to zero with the hexadecyl derivative (22). The butyl derivative was not seriously affected by serum but no *in vivo* activity could be demonstrated in guinea-pigs. No favourable effect was produced by the introduction of a 3-(2-diethylaminoethyl) group (23) or of a 4-phenyl or 4-*p*-butoxyphenyl group (24, 25, 26).

Late in 1946, the first information regarding parallel work which had been proceeding in Germany became available in this country. Behnisch (*Elberfeld Ann. Res. Reports*, No. 17, p. 2; FD 20/46) reported the activity of various substituted benzaldehyde thiosemicarbazones. In particular, *p*-pyrrolidino- and *o*-nitro-benzaldehyde thiosemicarbazones were mentioned as active, the latter having been selected for clinical test. The 3-ethyl*iso*thiosemicarbazones (27, 29) corresponding to these two compounds were therefore prepared together with *p*-dimethylaminobenzaldehyde thiosemicarbazone (28). None of these compounds showed promising activity, nor did *o*-nitrobenzaldehyde thiosemicarbazone itself. This is in agreement with the recent findings of Hoggarth, Martin, Storey, and Young (*Brit. J. Pharmacol.*, 1949, **4**, 248) who found no *in vivo* activity with *o*-nitrobenzaldehyde thiosemicarbazone or with 3-alkyl*iso*thiosemicarbazones in general. Subsequent publications (Domagk, Behnisch, Mietzsch, and Schmidt, *Naturwiss.*, 1946, **33**, 15; Domagk, *Zentr. Gynäk.*, 1947, **69**, 833) show that their approach to the thiosemicarbazones was almost identical with our own, starting in their case from the observation of the activity of 2-sulphanilamido-5-ethyl-1 : 3 : 4-thiadiazole (I; X = S,

TABLE II.

3-Alkylisothiosemicarbazones and 2-alkylisothioureas.

Compound.	R.	R'.	R''.	Hydrohalide. M. p.	Formula.	Found N, %	Req. N, %	Activity.‡ In absence of serum.	In presence of serum.
-*isothiosemicarbazone.*	RN:C(SR')·NHR''.								
(17) Acetone 3-ethyl-	$Me_2C{:}N-$	Et	H	153—154°	$C_6H_{13}N_3S,HCl$ *	21·35	21·5	10	10
(18) *Acetone 4-sulphanilyl-3-ethyl-*	$Me_2C{:}N-$	Et	$\cdot SO_2\cdot C_6H_4\cdot NH_2$-*p*	—	—	—	—	1	—
(19) Benzaldehyde 2-ethyl-	PhCH:N–	Et	H	193—194	$C_{20}H_{18}N_3S,HCl$	17·3	17·2	10	10—50
(20) Benzaldehyde 3-butyl-	PhCH:N–	C_4H_9	H	185—186	$C_{12}H_{17}N_3S,HCl$ *	15·7	15·5	100 (500)	50
(21) Benzaldehyde 3-octyl-	PhCH:N–	C_8H_{17}	H	176	$C_{16}H_{25}N_3S,HCl$ *	12·6	12·8	10	10
(22) Benzaldehyde 2-hexadecyl-	PhCH:N–	$C_{16}H_{33}$	H	162—163	$C_{24}H_{41}N_3S,HCl$ *	9·8	9·6	<1	—
(23) Benzaldehyde 3-(2-diethylaminoethyl)-	PhCH:N–	$NEt_2\cdot CH_2\cdot CH_2\cdot$	H	192	$C_{14}H_{22}N_4S,2HCl$ *	15·5	15·95	10	10
(24) *Benzaldehyde 4-phenyl-3-ethyl-*	PhCH:N–	Et	Ph	—	—	—	—	50 (100)	10
(25) Benzaldehyde 4-phenyl-3-(2-diethylaminoethyl)-	PhCH:N–	$NEt_2\cdot CH_2\cdot CH_2\cdot$	Ph	—	—	—	—	10	5—10
(26) *Benzaldehyde 4-p-butoxyphenyl-3-ethyl-*	PhCH:N–	Et	*p*-$C_4H_9O\cdot C_6H_4\cdot$	—	—	—	—	10	—
(27) *p*-Pyrrolidinobenzaldehyde 3-ethyl-	*p*-$[CH_2]_4>N\cdot C_6H_4\cdot CH{:}N-$	Et	H	245 †	$C_{14}H_{20}N_4S,HCl$ *	17·7	17·9	(50)	—
(28) *p*-Dimethylaminobenzaldehyde 3-ethyl-	*p*-$Me_2N\cdot C_6H_4\cdot CH{:}N-$	Et	H	230—232	$C_{13}H_{18}N_4S,HCl$ *	19·8	19·5	1	—
(29) *o*-Nitrobenzaldehyde 3-ethyl-	*o*-$NO_2\cdot C_6H_4\cdot CH{:}N-$	Et	H	169·5—170·5	$C_{10}H_{12}O_2N_4S,HCl$ *	19·2	19·4	(10)	—
-*isothiourea.*									
(30) *N*-Phenyl-*S*-ethyl-	Ph	Et	H	—	—	—	—	>500	1—5
(31) *N*-Phenyl-*S*-butyl-	Ph	C_4H_9	H	—	—	—	—	100	10 (50)
(32) *N*-Phenyl-*S*-octyl-	Ph	C_8H_{17}	H	—	—	—	—	50	5
(33) *N*-*p*-Butoxyphenyl-*S*-ethyl-	*p*-$C_4H_9O\cdot C_6H_4\cdot$	Et	H	—	—	—	—	1—5	1—5
(34) *NN'*-Diphenyl-*S*-ethyl	Ph	Et	Ph	—	—	—	—	100 (500)	1—5
(35) *S*-Methyl-	H	Et	H	115—117	$C_6H_{14}N_2SHI$	—	—	—	<1
(36) *S*-Butyl-	H	C_4H_9	H	109—110	$C_8H_{18}N_2S,HI$ *	11·0	10·6	—	5
(37) *S*-Octyl	H	C_8H_{17}	H	96—96·5	$C_{12}H_{26}N_2S,HBr$ *	10·85, 10·7	10·4	—	1

* New compound. † With decomposition.

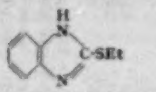
‡ See Notes to Table I. Figures in parentheses represent dilutions at which partial inhibition occurred.

(17) Needles from acetone. (18) See Experimental. (19) Baird *et al.* (*loc. cit.*) record m. p. 193°. (20) Colourless rods from ethanol–acetone. (21) Shining plates from acetone. (22) Needles from acetone–methanol. (23) Hygroscopic plates from acetone–ethanol. (24) The free base crystallised from ethanol in large pale yellow plates, m. p. 78° (Found: N, 14·85. $C_{17}H_{17}N_3S$ requires N, 14·85%). (25) The *Reinechate*, crystallised from 40% acetone, had m. p. 166—167° (decomp.) (Found: N, 20·7. $C_{28}H_{33}N_{10}S_2Cr$ requires N, 20·8%). For test this was converted into an aqueous solution of the hydrochloride. (26) The free *base* crystallised from ethanol in plates, m. p. 90° (Found: N, 12·2. $C_{20}H_{24}ON_2S$ requires N, 11·8%). It was feebly basic. (27) Reddish-brown needles from ethanol. (28) The *dihydrochloride* crystallised from ethanol containing a little hydrogen chloride in yellow needles, m. p. 210—220° (decomp.) (Found: N, 17·85. $C_{12}H_{20}N_4Cl_2S$ requires N, 17·3%), converted into red needles of the monohydrochloride by boiling with ethanol. (29) Irregular crystals from ethanol containing a little hydrogen chloride. (30) The picrate, yellow needles from 70% ethanol, had m. p. 190·5° (Found: N, 17·4. Calc. for $C_{15}H_{15}O_7N_5S$: N, 17·1%). Bertram (*Ber.*, 1892, **25**, 55) records m. p. 196°. (31) The *picrate*, yellow plates from ethanol, had m. p. 144° (Found: N, 16·2. $C_{19}H_{23}O_7N_5S$ requires N, 16·0%). (32) The *picrate*, minute yellow needles from ethanol, had m. p. 130·5° (Found: N, 14·5. $C_{21}H_{27}O_7N_5S$ requires N, 14·2%). (33) The *picrate*, large yellow prisms from ethanol, had m. p. 162—163° (Found: N, 14·9. $C_{18}H_{22}O_8N_5S$ requires N, 14·35%). (34) The free base, crystallised from aqueous ethanol, had m. p. 73° (Found: N, 11·1. Calc. for $C_{16}H_{18}N_2S$: N, 10·95%. Will (*Ber.*, 1881, **14**, 1490) records m. p. 79° and Rathke (*ibid.*, p. 1777) records m. p. 78°. (35) Bernthsen and Klinger (*Ber.*, 1878, **11**, 492) record m. p. 117°. (36) Plates from chloroform. (37) Plates from chloroform–ether.

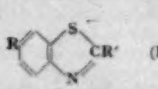
R = H, R′ = Et). It is now clear that, notwithstanding the apparent logic of the approach, the activities of the thiadiazoles and thiosemicarbazones are in fact entirely unrelated. Thus, while the oxa- and thia-diazoles are equally active, semicarbazones, in contrast with the corresponding thiosemicarbazones, are entirely inactive (Behnisch, Mietzsch, and Schmidt, *Angew. Chem.*, 1948, **60**, 113; Hoggarth *et al.*, *loc. cit.*). Further, while the sulphanilamido-group is essential to the activity of the oxa- and thia-diazoles, it greatly reduces the activity in the case of *iso*thiosemicarbazones as noted above. The fact that the *iso*thiosemicarbazones are more closely related structurally to the thiadiazoles than are the thiosemicarbazones is therefore without significance. The latter structure is apparently more favourable in this series to the development of *in vivo* activity, in spite of the approximately equivalent *in vitro* activity of the two types of compound. Our own subsequent trials have confirmed the high *in vivo* activity of selected members of the thiosemicarbazone group (Domagk, *Nordisk Medicin*, 1948, **39**, 1322; Hoggarth *et al.*, *loc. cit.*).

As a further simplification of the basic structure, *S*-alkyl*iso*thioureas, prepared by standard methods, were next examined. Very high *in vitro* activity was shown by *N*-phenyl- and *NN*′-diphenyl-*S*-ethyl*iso*thioureas (**30**, **34**). This was reduced in the former case by substitution of *S*-butyl and *S*-octyl groups (**31**, **32**) for ethyl or by introduction of a *p*-butoxy-group into the *N*-phenyl substituent (**33**). This series was not extended, since poor activity in the presence of serum precluded *in vivo* activity.

2-Ethylthiobenziminazole (III), which may be regarded as a cyclic *iso*thiourea, was prepared from 2-mercaptobenziminazole (Billeter and Steiner, *Ber.*, 1887, **20**, 231) by interaction with ethyl iodide. It was only weakly active. 2-Aminobenzthiazoles may also be regarded as cyclic *iso*thioureas, and the claims of Freedlander and French (*Proc. Soc. Exp. Biol. Med.*, 1947, **66**, 362) that *in vivo* activity had been demonstrated with such compounds and with related 2-alkoxybenzthiazoles prompted us to examine a selection of these compounds.



(III.)



(IV.)

2 : 6-Diaminobenzthiazole (IV; R = R′ = NH_2), stated to be one of the most active compounds, was prepared by the method of Kaufmann and Schultz (*Arch. Pharm.*, 1935, **273**, 31). It had relatively low *in vitro* activity and no *in vivo* activity. 2-Amino-6-butoxybenzthiazole (IV;

TABLE III.

2-Alkylthiopyrimidines.

Pyrimidine.	B. p.	M. p.	Formula.	Found N, %.	Req. N, %.
(38) 2-Mercapto-4 : 6-dimethyl-	—	209—212°	—	—	—
(39) 2-Methylthio-4 : 6-dimethyl-	113—114°/15 mm.	27—28	$C_7H_{10}N_2S$	19·2	18·2
(40) 2-*Methylthio*-4-*phenyl*-6-*methyl*-	154—160°/1 mm.	—	$C_{12}H_{12}N_2S$	13·0	13·0
(41) 4-Hydroxy-2-methylthio-6-methyl-	—	224—225	—	—	—
(42) 4-Hydroxy-2-methylthio-5-methyl-	—	234·5—236	—	—	—
(43) 4-*Hydroxy*-2-*butylthio*-5-*methyl*-	—	105—106	$C_9H_{14}ON_2S$	14·5, 14·3	14·1
(44) 4-*Hydroxy*-2-*octylthio*-5-*methyl*-	—	88—89	$C_{13}H_{22}ON_2S$	11·1	11·0
(45) 4-Chloro-2-methylthio-6-methyl-	118—120°/12 mm.	34—34·5	—	—	—
(46) 4-*Chloro*-2-*methylthio*-6-*methyl*-	132°/15 mm.	20—23	$C_6H_7N_2ClS$	15·9	16·0
(47) 4-*Chloro*-2-*butylthio*-5-*methyl*-	124—126°/1 mm.	—	$C_9H_{13}N_2ClS$	12·6	12·9
(48) 4-*Chloro*-2-*octylthio*-5-*methyl*-	144—145°/2 mm.	—	$C_{13}H_{21}N_2ClS$	10·5	10·2
(49) 4-Amino-2-methylthio-6-methyl-	—	135—136	—	—	—
(50) 4-*Amino*-2-*methylthio*-5-*methyl*-	—	130—131	$C_6H_9N_3S$	27·4	27·1
(51) 4-*Amino*-2-*butylthio*-5-*methyl*-	—	85—86	$C_9H_{15}N_3S$	21·5	21·3
(52) 4-*Amino*-2-*octylthio*-5-*methyl*-	—	85—86	$C_{13}H_{23}N_3S$	16·7	16·6

(38) Evans (*J. pr. Chem.*, 1903, **68**, 489) records m. p. 210°. (39) Hale and Williams (*J. Amer. Chem. Soc.*, 1915, **37**, 594) record m. p. 24°. Wheeler and Merriam (*Amer. Chem. J.*, 1904, **32**, 356) record m. p. 23—24° and b. p. 123—125°/14 mm. (41) Wheeler and Merriam (*ibid.*, 1903, **29**, 478) record m. p. 219°. (42) *Idem*, *ibid.*, record m. p. 233°. (43) Rods from ethanol. (44) Rhombic plates from methanol. (45) Wheeler and McFarland (*loc. cit.*) record b. p. 147°/32—35 mm., needles (from light petroleum), m. p. 39—40°. (49) Backer and Grevenstuk (*Rec. Trav. chim.*, 1945, **64**, 115) and Hull, Lovell, Openshaw, and Todd (*J.*, 1947, 41) record 136—137° and 133·5—135° respectively. (50) Clusters of rods from water. (51) Thin plates from benzene. (52) Irregular plates from light petroleum.

R = OBu, R' = NH_2), probably identical with the "*p*-butoxyaminobenzthiazole" described in F.P. 742,398, was prepared by the same procedure and was also devoid of activity. Attempted preparation of 6-amino-2-butoxybenzthiazole by the reduction of 6-*nitro*-2-*butoxybenzthiazole* with stannous chloride led to simultaneous chlorination with the formation of x-*chloro*-6-*amino*-2-*butoxybenzthiazole dihydrochloride*, also quite inactive.

Finally, as a further variant of alkylisothioureas, a number of substituted 2-alkylthiopyrimidines were prepared. These are summarised in Table III. In the preparation of 2-mercapto-4-phenyl-6-methylpyrimidine (Merkatz, *Ber.*, 1919, **52**, 869) as an intermediate for the 2-*methylthio*-derivative (40), an alkali-insoluble by-product was obtained and identified as *di*-(4-*phenyl*-6-*methyl*-2-*pyrimidyl*) *disulphide*, the same product being produced by oxidation of the mercaptopyrimidine with iodine. Condensation of the appropriate 2-alkylisothiourea with ethyl α-formylpropionate according to the method of Wheeler and Merriam (*Amer. Chem. J.*, 1903, **29**, 478) afforded 4-hydroxy-2-methylthio-, -2-*butylthio*-, and -2-*octylthio*-5-*methylpyrimidines* (42, 43, 44). These were converted smoothly into the 4-*chloro*-derivatives (46, 47, 48) by phosphorus pentachloride and phosphorus oxychloride (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431) and thence by ethanolic ammonia into the 4-*amino*-derivatives (50, 51, 52). The corresponding 2-methylthio-6-methylpyrimidines (41, 45, 49) were also prepared. All compounds except the intermediate chloro-derivatives were tested *in vitro*. Activities are not recorded since in no case were the compounds active at a dilution greater than 1 in 1000 in the presence of serum.

Experimental.

N^4-*Acyl Derivatives of* 2-*Sulphanilamido*-5-*methyl*-1 : 3 : 4-*oxadiazole*.—These were prepared by the condensation of 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole with the corresponding acid anhydride in benzene solution in the case of the *hexoyl* derivative, and with the corresponding acid chloride in pyridine solution in the case of the *dodecoyl* and *stearoyl* derivatives. The *toluene*-*p*-*sulphonyl* derivative was similarly prepared in pyridine. The products were crystallised from ethanol.

2-*Amino*-5-*alkyl*-1 : 3 : 4-*oxadiazoles*.—1-Acylthiosemicarbazides were prepared by heating a mixture of powdered thiosemicarbazide (1 mol.) with the appropriate acid anhydride (1 mol.) at 80° and finally at 110—120°. The product was triturated with ether or ethanol–ether and crystallised from ethanol. This afforded an impure product which was, however, satisfactory for the next stage. The crude acylthiosemicarbazide (10·0 g.) was stirred and heated under reflux with absolute ethanol (150—200 c.c.) and lead monoxide (3 mols.) for 15—30 hours. The lead sulphide and unchanged lead oxide were filtered off, the ethanol was removed *in vacuo*, and the solid residue triturated with aqueous sodium hydroxide to remove unchanged acylthiosemicarbazide. The residue was crystallised from ethanol–ether. In the case of 1-stearoylthiosemicarbazide the yield was poor owing to the formation of an insoluble lead salt of the thiosemicarbazide. Some improvement was effected by conducting the reaction in propanol instead of ethanol.

2-*Sulphanilamido*-5-*alkyl*-1 : 3 : 4-*oxadiazoles*.—The 2-amino-5-alkyloxadiazole was heated with acetylsulphanilyl chloride (1 mol.) in dry pyridine at 100° for 20—45 minutes, and the mixture poured into excess of dilute hydrochloric acid. The crude N^4-acetyl derivative was filtered off and hydrolysed in the usual manner with boiling 2*N*-sodium hydroxide. The crude product, obtained by acidification with hydrochloric acid, was purified by crystallisation from ethanol or aqueous ethanol.

2-*Sulphanilamido*-5-*amyl*-1 : 3 : 4-*thiadiazole*.—1-Hexoylthiosemicarbazide (22 g.) and benzenesulphonic acid (30 g., 1·25 mols.) were heated on the steam-bath for 15 minutes. The melt was cooled and dissolved in water, and the clear solution basified with ammonia. The precipitated solid was crystallised from ethanol, affording 2-*amino*-5-*amyl*-1 : 3 : 4-*thiadiazole* (17 g.) as needles, m. p. 195° (Found: N, 24·8. $C_7H_{13}N_3S$ requires N, 24·6%). The N^4-*acetylsulphanilyl* and *sulphanilyl* derivatives (see Table I) were prepared by the same methods as for the oxadiazoles and were both crystallised from ethanol.

2-(3 : 5-*Di-iodosulphanilamido*)-5-*methyl*-1 : 3 : 4-*oxadiazole*.—2-Sulphanilamido-5-methyloxadiazole (2·5 g.) was dissolved in water (15 c.c.) and concentrated hydrochloric acid (4 c.c.), and a solution of iodine monochloride (3·3 g.) in concentrated hydrochloric acid (3 c.c.) added. The solution soon became turbid and deposited a dark oil which solidified when warmed and scratched. The solid was filtered off, dried, and crystallised from ethanol. Yield, 3·0 g. (see Table I).

Benzaldehyde 4-*p*-*Butoxyphenylthiosemicarbazone*.—Following the general method for the preparation of aryl*iso*thiocyanates (*Org. Synth.*, Coll. Vol. I, 1941, p. 448), *p*-butoxyaniline (33 g.) was mixed with carbon disulphide (24 g.) with ice-cooling. Considerable heat was evolved, and the mixture solidified. Ethanol (36 c.c.) was added and after 2 hours the solid was broken up and cooled to 10°. Concentrated aqueous ammonia (33 g.) was then added at 10—15° in small portions with vigorous shaking. The solid dissolved and the ammonium salt of the dithiocarbamate crystallised. After being kept overnight, the crystals were filtered off, washed with ether (2 × 20 c.c.), and dissolved in water (400 c.c.). Addition of a solution of lead nitrate (70 g.) in water (200 c.c.) caused rapid precipitation of lead sulphide. The reaction was completed by boiling and the *p*-butoxyphenyl *iso*thiocyanate (11·25 g., 27%) isolated by extraction with ether as a mobile, odourless oil. The crude product (4·25 g.) in absolute ethanol (6 c.c.) was treated with hydrazine hydrate (1·2 c.c. of 90%) in ethanol (1 c.c.) with cooling. 4-*p*-Butoxyphenylthiosemicarbazide separated immediately in plates (4·2 g.), m. p. 175°. The crude product was heated under reflux for 3 hours with ethanol (60 c.c.) and benzaldehyde (2·2 g.). After filtration from a little undissolved solid, the solution on concentration afforded *benzaldehyde* 4-*p*-*butoxyphenylthiosemi-*

carbazone (4·5 g.) as pale yellow needles, m. p. 164—165° after recrystallisation from ethanol (Found: N, 12·9. $C_{11}H_{11}ON_3S$ requires *N*, 12·85%).

3-Alkylisothiosemicarbazones.—These were prepared from the corresponding thiosemicarbazones by alkylation with sodium ethoxide and the appropriate alkyl halide in ethanol (Baird, Burns, and Wilson, *loc. cit.*). The hydrochlorides were formed by precipitation of the crude bases in ether with hydrogen chloride and by crystallisation of the product from a suitable solvent (see Table II).

Acetone 4-N¹-Acetylsulphanilyl-3-ethylisothiosemicarbazone.—Acetone 3-ethylisothiosemicarbazone (3·2 g.) was stirred with 50% ethanol (25 c.c.) and sodium hydrogen carbonate (2·1 g.), and acetylsulphanilyl chloride (5·13 g., 1·1 mols.) was added at 20°. The viscous oil, which separated on stirring of the mixture overnight, afforded a granular solid on trituration with ether containing a little ethanol. Crystallisation from ethanol yielded crude *acetone 4-N¹-acetylsulphanilyl-3-ethylisothiosemicarbazone* (0·67 g.) as prisms, m. p. 167—168° raised by repeated recrystallisation from ethanol and from acetic acid to 183—184° (Found: N, 15·8. $C_{14}H_{20}O_3N_4S_2$ requires N, 15·7%).

When sodium hydroxide was used instead of sodium hydrogen carbonate the sole product obtained was ethyl acetylsulphanilate, plates (from aqueous ethanol), m. p. 121—122° (Found: N, 5·9. Calc. for $C_{20}H_{11}O_4NS$: N, 5·6%). Crossen, Jenkins, and Rogers (*Pharm. Arch.*, 1941, **12**, 26) quote m. p. 121°. Hydrolysis afforded sulphanilic acid, identified by colour reactions and analysis (Found: N, 8·0. Calc. for $C_6H_7O_3NS$: N, 8·1%).

Acetone 4-Sulphanilyl-3-ethylisothiosemicarbazone.—The foregoing compound (0·17 g.) was heated with 2-*N*-sodium hydroxide (1 c.c.) at 100° for 1 hour. Acidification to pH 4 afforded a precipitate of *acetone 4-sulphanilyl-3-ethylisothiosemicarbazone* (0·14 g.), prisms (from ethanol), m. p. 186—187° (Found: N, 17·9. $C_{11}H_{18}O_2N_4S$ requires *N*, 17·6%).

N-p-Butoxyphenylthiourea.—*p*-Butoxyphenyl *iso*thiocyanate (7·0 g.) in ethanol (20 c.c.) was treated with gaseous ammonia with cooling until no further crystalline material separated. The product (7·5 g.) was crystallised from ethanol, giving *N-p-butoxyphenylthiourea* as rods, m. p. 163° (Found: N, 12·4. $C_{11}H_{16}ON_2S$ requires N, 12·5%).

S-Alkylisothioureas.—These were prepared from the appropriate thiourea and alkyl halide in refluxing ethanol. The resulting alkylisothiourea hydrohalides were tested as such or converted into picrates and thence into aqueous solutions of the hydrochlorides for test.

2-Ethylthiobenziminazole.—2-Mercaptobenziminazole (Billeter and Steiner, *loc. cit.*) (1·5 g.), suspended in ethanol (5 c.c.), was heated under reflux with ethyl iodide (1·6 g.) for 2 hours, complete dissolution occurring after 15 minutes. The ethanol was evaporated *in vacuo* and the crystalline residue (2·85 g.) dissolved in water, the solution filtered, and the free base precipitated with sodium carbonate solution. Recrystallisation of the resulting white solid from aqueous ethanol afforded *2-ethylthiobenziminazole* as needles, m. p. 173·5—174·5° (Found: N, 15·9. $C_9H_{10}N_2S$ requires N, 15·7%).

*2-Amino-6-butoxybenzthiazole.**—A solution of bromine (10 g.) in glacial acetic acid (13 c.c.) was added slowly with stirring to a solution of *p*-butoxyaniline (8·25 g.) and ammonium thiocyanate (9·5 g.) in 95% acetic acid (50 c.c.). The yellow solid which separated overnight was filtered off and the filtrate diluted with water. Addition of aqueous sodium hydroxide caused first the separation of a dark oil, which was discarded, and then a solid (2·2 g.), m. p. 101°. Repeated crystallisation from carbon tetrachloride afforded 2-amino-6-butoxybenzthiazole as prisms, m. p. 119° (Found: N, 12·7. Calc. for $C_{11}H_{14}ON_2S$: N, 12·6%). F.P. 742,398 cites m. p. 121° for "*p*-butoxyaminobenzthiazole".

*x-Chloro-6-amino-2-butoxybenzthiazole Dihydrochloride.**—2-Chloro-6-nitrobenzthiazole was prepared by the method of Hofmann (*Ber.*, 1880, **13**, 10) from 2-chlorobenzthiazole (Scott and Watt, *J. Org. Chem.*, 1937, **2**, 148). This (10 g.) was dissolved in warm butanol (250 c.c.), a solution of sodium (1·07 g.) in butanol (50 c.c.) added, and the mixture boiled under reflux for 20 hours. After filtration, the solution was evaporated to a small volume, affording *6-nitro-2-butoxybenzthiazole* (4·15 g.), needles (from chloroform), m. p. 60° (Found: N, 11·2. $C_{11}H_{12}O_3N_2S$ requires N, 11·1%). The foregoing (10 g.) was added to a preheated solution of crystalline stannous chloride (32 g.) in concentrated hydrochloric acid (40 c.c.) at such a rate as to maintain the temperature at 70—80°. The reaction was completed by boiling under reflux for 30 minutes. The solution was then poured into 6*N*-sodium hydroxide (200 c.c.), and the solution extracted with butanol (4 × 50 c.c.). The combined extracts were dried (K_2CO_3) and hydrogen chloride passed in. The precipitated solid (2·5 g.) was recrystallised from aqueous ethanol, giving *x-chloro-6-amino-2-butoxybenzthiazole dihydrochloride* as needles, m. p. 268° (decomp.) (Found: N, 8·5, 8·7; Cl, 35·4. $C_{11}H_{15}ON_2Cl_3S$ requires N, 8·5; Cl, 32·3%). It dissolved in water to give a solution of low pH which could be adjusted to pH 6 without precipitation.

Di-(4-phenyl-6-methyl-2-pyrimidyl) Disulphide.—In the preparation of 2-mercapto-4-phenyl-6-methylpyrimidine (Merkatz, *loc. cit.*) a fraction was obtained which was insoluble in ethanol and in dilute hydrochloric acid or sodium hydroxide. It was purified by exhaustive extraction with N-hydrochloric acid. Crystallisation from benzene afforded *di-(4-phenyl-6-methyl-2-pyrimidyl) disulphide* as yellow rods, m. p. 185·5—186° (Found: N, 13·9; *M*, 397. $C_{22}H_{18}N_4S_2$ requires N, 13·9; *M*, 402). The same compound, m. p. 184—184·5° not depressed by the above, was formed when a solution of the mercaptopyrimidine in dilute sodium hydroxide was oxidised with a slight excess of aqueous iodine solution.

4-Hydroxy-2-alkylthio-5-methylpyrimidines.—The appropriate *S*-alkylisothiourea hydrohalide (1 mol.) was dissolved in one equivalent of 2·5*N*-sodium hydroxide, and, if necessary, ethanol was added to dissolve precipitated oil or solid. Crude ethyl sodioformylpropionate (1 mol.) was then added with sufficient water to give a clear solution. After 24 hours the solution, filtered if necessary, was acidified with acetic acid, and the product dried and crystallised (see Table III).

4-Chloro-2-alkylthio-5-methylpyrimidines.—The 4-hydroxypyrimidine was boiled under reflux with a mixture of phosphorus pentachloride (1 mol.) and an equal weight of phosphorus oxychloride for 45 minutes. Phosphorus oxychloride was distilled off *in vacuo* and the residue poured on crushed ice. The crude solid or oil was isolated with ether and distilled (see Table III).

* Experiments by Mr. J. L. Lowe.

4-Amino-2-alkylthio-5-methylpyrimidines.—The chloropyrimidine was heated under pressure at 135—150° with 10% ethanolic ammonia (ca. 6—10 parts by weight) for 6—8 hours. The ammonium chloride which separated on cooling was filtered off and the filtrate evaporated. The residue was dissolved in dilute acetic acid, and the product precipitated as a solid by the addition of aqueous sodium hydroxide and crystallised from a suitable solvent (see Table III).

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RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD., NOTTINGHAM.

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91. *Antituberculous Compounds. Part VI.* p-(ω-Alkoxyalkoxy)-N-arylbenzamidines and Analogues.

By F. C. COOPER and M. W. PARTRIDGE.

A series of *p*-(ω-alkoxyalkoxy)-*N*-arylbenzamidines and certain analogues have been prepared. Comparison of their activities *in vitro* against *Mycobacterium tuberculosis* with those of the diamidines and of the monoamidines described in Parts II and III respectively (*J.*, 1949, 2683, 3043) has extended the earlier observations on the differences in the relation between structure and activity in analogous monoamidines and diamidines and on the significance of the *N*-aryl substituents. Isosteric replacement of methylene by oxygen in the monoamidines apparently causes a marked decrease in activity.

MARKED activity *in vitro* against *Mycobacterium tuberculosis* by di-(*p*-*N*-arylamidinophenoxy)-alkanes (I) and *p*-alkoxy-*N*-arylbenzamidines (II) has been reported in Parts II and III (*J.*, 1949, 2683, 3043) respectively. In these two series, differences were observed in the effects on *in vitro* activity of (*a*) homology in the polymethylene chain of the diamidines and in the alkoxy-group of the monoamidines, (*b*) substitution in the *N*-aryl groups, and (*c*) the presence of serum in the medium during testing. In this communication further experiments on monoamidines are described.

Additional information on the relation between homology and activity was sought through a series of *p*-2-alkoxyethoxy-*N*-phenylbenzamidines (III; $n = 2$, R = alkyl, R′ = Ph). Changes in activity induced by substitution in the *N*-phenyl substituent of the amidine group and by replacement of the *N*-phenyl group by analogous ring systems were also examined in the same series. The preparation of certain analogues of (III) made possible some examination of the significance of the important functional groups in the monoamidine and diamidine series, and of the effect produced by the isosteric replacement of methylene by oxygen.

(I.) Ar·NH·C(:NH)·C$_6$H$_4$·O·[CH$_2$]$_n$·O·C$_6$H$_4$·C(:NH)·NHAr

RO·C$_6$H$_4$·C(:NH)·NHAr (II.)

RO·[CH$_2$]$_n$·O·C$_6$H$_4$·C(:NH)·NHR′ (III.)

The 2-alkoxyethanols described in the Experimental section were obtained in satisfactory yield by the method of Palomaa (*Ber.*, 1902, **35**, 3299); in a number of instances, the corresponding diether of ethylene glycol, as would be expected, was formed as a by-product. We find that 2-dodecyloxyethanol, which is claimed by Halasz (*Bull. Soc. chim.*, 1941, **8**, 170) to have been prepared in very low yield and to have m. p. 51°, has m. p. 22—24°. The values said to have been found and required for the elementary analysis correspond to the composition not of 2-dodecyloxyethanol ($C_{14}H_{30}O_2$) but of a compound, $C_{14}H_{30}O$; recalculation of the published results is not possible because of a misprint in the analytical data; it is unlikely that Halasz's material was 1 : 2-*didodecyloxyethane* ($C_{38}H_{54}O_2$) which we find has m. p. 37—38°. Conversion of the 2-alkoxyethanols into the corresponding chlorides or bromides was readily effected by the procedures of Bennett and Heathcoat (*J.*, 1929, 268) and of Palomaa and Kenetti (*Ber.*, 1931, **64**, 797) respectively. It was difficult to obtain consistent elementary analyses of these alcohols and halides; their purity was therefore checked by determination of the molecular refractions.

The preparative work involved in the production of the substituted phenyl cyanides afforded

	Base.					Picrate.				Activity.*	
	Yield, %	M. p.	Formula.	Found N, %	Req., N, %	M. p.	Formula.	Found N, %	Req., N, %	In absence of serum.	In presence of serum.
1. p-(2-*Methoxyethoxy*)-N-*phenylbenzamidine* ...	85	124—125°	$C_{16}H_{18}O_2N_2$	10·35	10·35	96—98°	$C_{22}H_{21}O_9N_5$	13·9	14·0	5	1
2. p-(2-*Ethoxyethoxy*)-N-*phenylbenzamidine* ...	73	121—121·5	$C_{17}H_{20}O_2N_2$	9·85	9·85	82—84	$C_{23}H_{23}O_9N_5$	13·3	13·65	10	10
3. p-(2-*Propoxyethoxy*)-N-*phenylbenzamidine* ...	97	104—104·5	$C_{18}H_{22}O_2N_2$	9·45	9·4	84—86	$C_{24}H_{25}O_9N_5$	13·1	13·3	5—10	10
4. p-(2-*Butoxyethoxy*)-N-*phenylbenzamidine*	99	98—99	$C_{19}H_{24}O_2N_2$	9·1	8·95	79—81	$C_{25}H_{27}O_9N_5$	13·05	12·95	50	10—50
5. p-(2-*Amyloxyethoxy*)-N-*phenylbenzamidine* ...	85	93—94	$C_{20}H_{26}O_2N_2$	8·65	8·6	83—85	$C_{26}H_{29}O_9N_5$	12·5	12·6	50—100	10
6. p-(2-*Hexyloxyethoxy*)-N-*phenylbenzamidine* ...	43	97—98	$C_{21}H_{28}O_2N_2$	8·4	8·25	73—76	$C_{27}H_{31}O_9N_5$	12·4	12·3	50	10—50
7. p-(2-*Heptyloxyethoxy*)-N-*phenylbenzamidine*	44	97—98	$C_{22}H_{30}O_2N_2$	8·05	7·9	78—80	$C_{28}H_{33}O_9N_5$	11·8	12·0	—	10
8. p-(2-*Octyloxyethoxy*)-N-*phenylbenzamidine* ...	49	97—98	$C_{23}H_{32}O_2N_2$	7·9	7·6	76—78	$C_{29}H_{35}O_9N_5$	11·45	11·7	10	10—50
9. p-(2-*Dodecyloxyethoxy*)-N-*phenylbenzamidine*	75	98—99	$C_{27}H_{40}O_2N_2$	6·9	6·6	72—74	$C_{33}H_{43}O_9N_5$	10·75	10·7	—	<1 (10)
10. p-(2-*Hydroxyethoxy*)*benzamidine*	—	—	—	—	—	—	—	—	—	<1	—
11. p-(2-*Hydroxyethoxy*)-N-*phenylbenzamidine* ...	87	158—160	$C_{15}H_{16}O_2N_2$	10·7	10·95	164—165·5	$C_{21}H_{19}O_9N_5$	14·3	14·45	10—50	5—10
12. p-(2-*Ethoxyethoxy*)*benzamidine*	—	—	—	—	—	—	—	—	—	<1—1	<1—1
13. p-(3-*Ethoxypropoxy*)-N-*phenylbenzamidine* ...	60	85—87	$C_{18}H_{22}O_2N_2$	9·5	9·4	97—99	$C_{24}H_{25}O_9N_5$	13·0	13·3	50	10—50
14. p-(2-*Phenoxyethoxy*)-N-*phenylbenzamidine* ...	48	203—205	$C_{21}H_{20}O_2N_2$	8·6	8·4	—	—	—	—	<1	—
15. p-(3-*Phenoxypropoxy*)-N-*phenylbenzamidine*	61	128—129	$C_{22}H_{22}O_2N_2$	8·0	8·1	—	—	—	—	500	10
16. p-(2-*Methoxyethoxy*)-N-p'-*propoxyphenyl*-*benzamidine*	95	132—133	$C_{19}H_{24}O_3N_2$	8·8	8·55	97—99	$C_{25}H_{27}O_{10}N_5$	12·7	12·55	—	10
17. p-(2-*Ethoxyethoxy*)-N-p'-*propoxyphenylben*-*zamidine*	96	122—123	$C_{20}H_{26}O_3N_2$	8·45	8·2	137—139	$C_{26}H_{29}O_{10}N_5$	12·55	12·25	10	10
18. p-(2-*Ethoxyethoxy*)-N-p'-*chlorophenylben*-*zamidine*	84	115—116	$C_{17}H_{17}O_2N_2Cl$	9·15	8·8	133—134	$C_{23}H_{22}O_9N_5Cl$	12·0	12·8	—	10—50
19. p-(2-*Ethoxyethoxy*)-N-*cyclohexylbenzamidine*	—	—	—	—	—	—	—	—	—	—	5
20. p-(2-*Ethoxyethoxy*)-N-2'-*pyridylbenzamidine*	—	—	—	—	—	—	—	—	—	—	10
21. p-(2-*Ethoxyethoxy*)-N-*benzylbenzamidine*	—	—	—	—	—	—	—	—	—	10	5—10
22. 3-Ethoxypropanol	—	—	—	—	—	—	—	—	—	—	<1
23. 2-Propoxyethanol	—	—	—	—	—	—	—	—	—	—	<1 (5)
24. 2-Butoxyethanol	—	—	—	—	—	—	—	—	—	—	<1
25. 2-Amyloxyethanol	—	—	—	—	—	—	—	—	—	—	<1
26. 2-*Hexyloxyethanol*	—	—	—	—	—	—	—	—	—	—	1
27. 2-*Heptyloxyethanol*	—	—	—	—	—	—	—	—	—	10	5—10
28. 2-*Octyloxyethanol*	—	—	—	—	—	—	—	—	—	10—50	5—10

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Figures in parentheses represent dilutions (in thousands) at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

(1), (2) Colourless needles. (3) Colourless plates. (4) Colourless plates. The *picrate* crystallised as yellow plates from aqueous methanol; from aqueous acetic acid, it separated as solvated needles, m. p. 100—102° after sintering at 84° (Found: loss at 55°/vac., 5·05. Found, on dried material, N, 12·7. $C_{22}H_{21}O_9N_5,0{\cdot}5C_2H_4O_2$ requires $C_2H_4O_2$, 5·25%. $C_{22}H_{21}O_9N_5$ requires N, 12·95%). (5) Colourless plates. (6) Colourless plates. The *benzenesulphonate*, colourless needles from benzene, had m. p. 138—139° (Found: C, 64·75; H, 6·7; N, 5·85. $C_{27}H_{30}O_5N_2S$ requires C, 65·05; H, 6·55; N, 5·6%). (7) Colourless plates. The *picrate* crystallised from aqueous ethanol as thin plates (Found: loss at 55°/vac., 2·8. $C_{28}H_{32}O_9N_5,H_2O$ requires H_2O, 3·0%). (8) Colourless plates. The *benzenesulphonate*, colourless needles from benzene, had m. p. 123—124° (Found: C, 65·8; H, 7·3; N, 5·6. $C_{26}H_{32}O_5N_2S$ requires C, 66·1; H, 7·25; N, 5·3%). (9) Colourless leaflets. The *picrate* crystallised from aqueous ethanol as solvated needles (Found: loss at 20°/vac., 2·6. $C_{33}H_{43}O_9N_5,H_2O$ requires H_2O, 2·7%). (11) Colourless prisms from *iso*propanol. The *amidinium chloride*, colourless prisms from water, had m. p. 143—145° (decomp.) (Found: loss at 100°/vac., 6·4. Found, on dried material, N, 9·45; Cl^-, 11·8; $C_{15}H_{17}O_2N_2Cl,H_2O$ requires H_2O, 5·8%. $C_{15}H_{16}O_2N_2,HCl$ requires N, 9·55; Cl^-, 12·1%). (13), (16) Colourless leaflets. (14) Colourless leaflets from 2-ethoxyethanol. (15) Colourless leaflets from xylene. (17) Colourless plates. The *picrate*, yellow plates from aqueous methanol, melted and effervesced at 110—112°, resolidified, and melted again at 138—139° when not previously dehydrated (Found: loss at 100°/vac., 4·3. $C_{26}H_{29}O_{10}N_5,1{\cdot}5H_2O$ requires H_2O, 4·5%). (18) Plates (Found: Cl, 10·95. $C_{17}H_{17}O_2N_2Cl$ requires Cl, 11·1%).

little new of chemical interest. For the preparation of the *N*-aryl-substituted amidines described in the table, the arylammonium benzenesulphonate method (Oxley and Short, *J.*, 1946, 147) was used; Pinner's method was applied in the preparation of the unsubstituted amidines, and the aluminium chloride method (Oxley, Partridge and Short, *J.*, 1947, 1110) to that of p-(2-*ethoxyethoxy*)-N-*cyclohexyl*-, -N-2'-*pyridyl*-, and -N-*benzyl-benzamidine*. The last compound was also obtained, but only in 3% yield, by interaction of benzylammonium thiocyanate and p-(2-*ethoxyethoxy*)*phenyl cyanide* (Partridge and Short, *J.*, 1947, 390). For the determination of activity *in vitro*, the *N*-substituted amidines were obtained in solution as their lactates.

The activities against *M. tuberculosis in vitro* are recorded in the table. The activity of members of the series of p-(2-*alkoxyethoxy*)-*N*-*phenylbenzamidines* (III; $n = 2$, R′ = Ph, R = Me, Et, Pr^n, Bu^n, n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}, or n-$C_{12}H_{25}$) increases gradually to a maximum when R is C_4—C_8 and then decreases with the higher homologues. In this respect, the series resembles the *p*-alkoxy-*N*-phenylbenzamidines and other series discussed in Part III but differs from the di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II). A large increase in activity in passing from the C_4 to the C_5 homologue, which was observed in the *p*-alkoxy-*N*-phenylbenzamidines, is not apparent here. There is some indication that the presence of serum in the medium during testing inhibits the activity to a lesser extent than in *p*-alkoxy-*N*-phenylbenzamidines, although this inhibiting effect of serum is more pronounced than with the di-(*p*-*N*-arylamidinophenoxy)alkanes. The outstanding feature of the *p*-(2-alkoxyethoxy)-*N*-phenylbenzamidines is their low activity compared with the analogous series described in Part III; this may be ascribed to the replacement of methylene by oxygen. Activities equal to or greater than that shown by 4-aminosalicylic acid, under the same conditions of test, are nevertheless retained.

The dyschemotherapeutic effect of the replacement of methylene by oxygen is best illustrated by a comparison of the isosteres, *p*-hexyloxy-*N*-phenylbenzamidine (Part III) (II; R = n-C_6H_{13}, Ar = Ph) and *p*-(2-propoxyethoxy)-*N*-phenylbenzamidine (III; $n = 2$, R = Pr^n, R′ = Ph) which are active at 1 : 5,000,000 and 1 : 5000—10,000 respectively. A similar but much less marked effect of this type of change in structure is to be observed in the series studied by Friedman *et al.* (*J. Pharm. Exp. Ther.*, 1947, **89**, 153). Some significance may possibly be attached to the position of this second ethereal oxygen atom, since the other isostere which was prepared, namely p-(3-*ethoxypropoxy*)-*N*-*phenylbenzamidine* (III; $n = 3$, R = Et, R′ = Ph) is active at 1 : 50,000. This feature and the 500-fold increase in activity in passing from p-(2-*phenoxyethoxy*)-*N*-*phenyl*- (III; $n = 2$, R = R′ = Ph) to p-(3-*phenoxypropoxy*)-*N*-*phenylbenzamidine* (III; $n = 3$, R = R′ = Ph) are reminiscent of the alternation in activity noted in di-(*p*-*N*-phenylamidinophenoxy)alkanes (I; $n = 2$, 3, 4, 5, or 6), in which members having an even number of methylene groups were inactive whereas members with an odd number were active.

A comparison of the activities of *p*-(3-ethoxypropoxy)-*N*-phenylbenzamidine, *p*-(3-phenoxypropoxy)-*N*-phenylbenzamidine, and 1 : 3-di-(*p*-*N*-phenylamidinophenoxy)propane (Part II) (I; $n = 3$, Ar = Ph) indicates that in these monoamidines replacement of the 3-ethyl by 3-phenyl enhances activity *in vitro*, but in order to maintain this activity in the presence of serum, a second *N*-phenyl-substituted amidine group is necessary. Replacement of the 2-ethoxy-group of *p*-(2-ethoxyethoxy)-*N*-phenylbenzamidine by hydroxyl (III; $n = 2$, R = H, R′ = Ph) produces no important change in activity, but the ten-fold decrease in activity which occurs in the corresponding unsubstituted *amidines* (III; $n = 2$, R = Et, R′ = H) and (III; $n = 2$, R = R′ = H) provides evidence additional to that noted in Parts II and III of the importance of the *N*-phenyl substituent in the amidine group. The introduction of *p*-propoxy- (III; $n = 2$; R = Me or Et, R′ = *p*-PrO·C_6H_4) and *p*-chloro- (III; $n = 2$, R = Et, R′ = *p*-C_6H_4Cl) groups into the *N*-phenyl groups of *p*-(2-methoxy- and 2-ethoxy-ethoxy)-*N*-phenylbenzamidines produces no important change in activity. As far as comparison is possible, this effect is in accord with what was found in corresponding *p*-alkoxy-*N*-arylbenzamidines reported in Part III and in contrast with the findings for di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II). The *N*-*cyclo*hexyl (III; $n = 2$, R = Et, R′ = $-\overline{\text{CH·CH}_2\text{·CH}_2\text{·CH}_2\text{·CH}_2\text{·CH}_2}$), *N*-2′-pyridyl (III; $n = 2$, R = Et, R′ = $-\overline{\text{C:N·CH:CH·CH:CH}}$), and *N*-benzyl (III; $n = 2$, R = Et, R′ = $-CH_2\text{·}C_6H_5$) analogues of *p*-(2-ethoxyethoxy)-*N*-phenylbenzamidine are of about the same order of activity as the parent compound.

From the results obtained with seven ω-alkoxyalkanols, it would appear that no special significance may be assigned to the activities of the *heptyl* and *octyl* homologues. Many similar

instances of long-chain compounds exhibiting activity against *M. tuberculosis in vitro* have been reported (see, *e.g.*, Walker and Sweeney, *J. Infect. Dis.*, 1920, **26**, 238; Stanley *et al.*, *J. Pharm. Exp. Ther.*, 1932, **45**, 121; Barry, *Nature*, 1946, **158**, 863; D'Arcy Hart, *Brit. Med. J.*, 1946, II, 805; 849; Suter, *Schweiz. med. Wschr.*, 1948, **78**, 324; Eiseman, *J. Exptl. Med.*, 1948, **88**, 189). The inhibiting effect of serum observed with the octyl homologue and its acute toxicity (2 mg./g. of body-weight by subcutaneous and by oral administration in mice) render it unlikely that any activity could be demonstrated *in vivo*.

Experimental.

2-Amyloxyethanol.—The following method derived from that of Palomaa (*loc. cit.*) was employed. Amyl bromide (151 g.) was gradually added to a solution of sodium (23 g., 1 atom) in hot ethylene glycol (200 g., 3·2 mols.), prepared in an atmosphere of nitrogen. The mixture, after boiling under reflux with stirring for 35 minutes, gave on distillation an azeotrope of ethylene glycol and 2-amyloxyethanol, containing 78% of 2-amyloxyethanol and having b. p. 180—182°/750 mm., d_4^{20} 0·9526, d_4^{25} 0·9499, n_D^{25} 1·4260. After being washed five times with water (50 c.c.), dried ($CaSO_4$), and re-fractionated, this material afforded 2-amyloxyethanol (56 g., 42%), b. p. 187—188°/753 mm., d_4^{20} 0·8926, d_4^{25} 0·8902, n_D^{25} 1·4239, $[R_L]_D$ 37·79 (calc., 37·85). Ashborn *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 1549) record b. p. 188·5°/751·1 mm., d^{25} 0·8893; Tallman (*ibid.*, 1934, **56**, 126) records d_4^{25} 0·8927; n_D^{25} 1·42233; Cretcher and Pittenger (*J. Amer. Chem. Soc.*, 1924, **46**, 1503) record b. p. 181°/745 mm. Low values for the b. p. (cf. also Berry and Michaels, *Quart. J. Pharm.*, 1947, **20**, 331) are probably attributable to an azeotrope of 2-amyloxyethanol with ethylene glycol.

2-Hexyloxyethanol.—Hexyl bromide (165 g.) was brought into reaction with a solution of sodium (23 g., 1 atom) in ethylene glycol (200 g., 3·2 mols.) in the same manner as for the foregoing compound, heating being for 2½ hours. The liquid, obtained free from sodium bromide by distillation under reduced pressure, was washed with water and dried ($CaSO_4$); on fractionation *2-hexyloxyethanol* (78 g., 53%), b. p. 110—112°/27 mm., was obtained (Found: C, 66·2; H, 12·0. $C_8H_{18}O_2$ requires C, 65·7; H, 12·4%), having d_4^{20} 0·8892, n_D^{20} 1·4291, and $[R_L]_D$ 42·40 (calc. 42·46). Berry and Michaels (*loc. cit.*) record, without further details, b. p. 89—93°/17 mm. for this compound. Interaction of ethylene chlorohydrin and sodium hexyloxide in xylene (cf. Cretcher and Pittenger, *loc. cit.*) failed to yield any material of constant b. p.

2-Heptyloxyethanol, prepared in 62% yield by the procedure described for the hexyl homologue, had b. p. 124—125°/28 mm. (Found: C, 66·8; H, 12·6. $C_9H_{20}O_2$ requires C, 67·45; H, 12·6%), d_4^{20} 0·8848, n_D^{20} 1·4325, $[R_L]_D$ 47·04 (calc. 47·15). 1 : 2-*Diheptyloxyethane* (9%), obtained from the end-run of the distillation, had b. p. 174—175°/19 mm. (Found: C, 73·8; H, 12·9. $C_{16}H_{34}O_2$ requires C, 74·35; H, 13·25%), d_4^{20} 0·8437, n_D^{20} 1·4330, $[R_L]_D$ 79·60 (calc. 79·92).

2-Octyloxyethanol.—Interaction of octyl bromide (193 g.) with ethylene glycol (200 g., 3·2 mols.) containing sodium (23 g., 1 atom) for 4 hours under conditions described for the amyl homologue, followed by distillation, afforded a two-phase distillate. The upper, water-insoluble layer was washed with water, and the washings were used in the recovery of a small quantity of water-insoluble material from the lower layer. The water-insoluble material, after being dried (K_2CO_3), yielded *2-octyloxyethanol* (90 g., 52%), b. p. 132—133°/22 mm. (Found: C, 68·55; H, 12·4. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·75%), d_4^{20} 0·8811, n_D^{20} 1·4357, $[R_L]_D$ 51·69 (calc. 51·74). This compound is referred to in F.P. 44,641 but no details are given. The end-run from the distillation afforded 1 : 2-*dioctyloxyethane* (7%), b. p. 188—191°/14 mm. (Found: C, 75·6; H, 12·85. $C_{18}H_{38}O_2$ requires C, 75·45; H, 13·35%), d_4^{20} 0·8455, n_D^{20} 1·4369, $[R_L]_D$ 89·76 (calc. 89·09).

2-Dodecyloxyethanol.—Prepared in 40% yield by the method described for the foregoing compound, this crystallised as colourless plates, which had m. p. 22—24°, depressed to 14—16° by dodecanol, and b. p. 142°/1·8 mm. (Found: C, 72·4; H, 12·3. Calc. for $C_{14}H_{30}O_2$: C, 73·0; H, 13·15%), d_4^{20} 0·8708, n_D^{20} 1·4432, $[R_L]_D$ 70·17 (calc. 70·33). Henkel et Cie (B.P. 401,142) record b. p. 170—174°/15 mm. The residue in the still contained 1 : 2-*didodecyloxyethane* (25%), colourless plates (from ethanol or *iso*propanol), m. p. 37—38° (Found: C, 78·45; H, 13·55. $C_{26}H_{54}O_2$ requires C, 78·3; H, 13·65%).

Halides.—2-Ethoxyethyl bromide was obtained by interaction of phosphorus tribromide, 2-ethoxyethanol, and pyridine by the method of Palomaa and Kenetti (*loc. cit.*) in 53% yield and had b. p. 126—127°/767 mm. (Vogel, *J.*, 1948, 644, records b. p. 128°/768 mm.). The method of *Org. Synth.*, 1943, **23**, 32, in our hands consistently failed to give better than 38% yield either of this compound or of 2-methoxyethyl bromide.

2-Propoxyethyl chloride. Interaction of thionyl chloride (78·5 g.), 2-propoxyethanol (62·5 g., 0·91 mol.), and dimethylaniline (87·2 g., 1·1 mols.) by the method of Bennett and Heathcoat (*loc. cit.*) afforded 2-propoxyethyl chloride (51 g., 69%), b. p. 129—131°/760 mm., n_D^{15} 1·4163 (Karvonen, *Ann. Acad. Sci. Fenn.*, 1912, *A*, **3**, No. 7, 1, gives b. p. 130°/756·3 mm., n_D^{15} 1·41756; Sklyarov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 2121, gives b. p. 119—120°, n_D^{20} 1·426). The method of Foran (*J. Soc. Chem. Ind.*, 1925, **44**, 173T) failed to give any of the desired product when applied to the preparation of 2-propoxyethyl bromide (cf. Bennett and Heathcoat, *loc. cit.*).

2-Butoxyethyl chloride, prepared in 66% yield by the procedure described for the foregoing compound, had b. p. 153—154°/755 mm., n_D^{15} 1·4220. Palomaa and Kenetti (*loc. cit.*) give b. p. 154·5°/750 mm., and Chalmers (*Canad. J. Research*, 1932, **7**, 464) gives b. p. 153—154°, whereas Sklyarov (*loc. cit.*) records b. p. 139—141° and n_D^{15} 1·431.

2-Amyloxyethyl chloride. After interaction of thionyl chloride (49 g.), 2-amyloxyethanol (49·6 g., 0·91 mol.), and dimethylaniline (55 g., 1·1 mols.) according to the method of Bennett and Heathcoat (*loc. cit.*), it was found advantageous to remove sulphur dioxide from the ethereal extract of the product by treatment with sodium hydrogen carbonate before drying, evaporation, and fractional distillation; yield, 37·2 g. (66%); b. p. 83—85°/35 mm., 174—175°/763 mm. (Found: C, 55·95; H, 10·3. $C_7H_{15}OCl$ requires C, 55·8; H, 10·05%); d_4^{20} 0·9363; n_D^{20} 1·4261; $[R_L]_D$ 41·22 (calc. 41·15).

2-Hexyloxyethyl bromide, prepared in 61% yield by the procedure of Palomaa and Kenetti (*loc. cit.*), had b. p. 121—122°/44 mm. (Found: C, 46·15; H, 7·45; Br, 37·6. $C_8H_{17}OBr$ requires C, 45·95; H, 8·2; Br, 38·2%). d_4^{20} 1·1558, n_D^{20} 1·4504, $[R_L]_D$ 48·66 (calc. 48·65).

2-Heptyloxyethyl bromide, prepared in 43% yield in the same way as the foregoing compound, had b. p. 132—135°/36 mm. (Found: C, 48·1; H, 8·4; Br, 35·6. $C_9H_{19}OBr$ requires C, 48·45; H, 8·6; Br, 35·8%). d_4^{20} 1·1298, n_D^{20} 1·4518, $[R_L]_D$ 53·27 (calc. 53·35).

2-Octyloxyethyl bromide, prepared in 51% yield in the same way, had b. p. 126—127°/14 mm. (Found: C, 50·0; H, 8·4; Br, 33·6. $C_{10}H_{21}OBr$ requires C, 50·6; H, 8·9; Br, 33·7%). d_4^{20} 1·1085, n_D^{20} 1·4526, $[R_L]_D$ 57·91 (calc. 57·93). The preparation of this compound is claimed in F.P. 44,641 but no confirmatory data are provided.

2-Dodecyloxyethyl bromide. A mixture of 2-dodecyloxyethanol (76·8 g.) and pyridine (5 g., 0·2 mol.) was added dropwise to phosphorus tribromide (36·1 g., 0·4 mol.) at 20—40°. After this had been kept overnight, water and ether were added; the ethereal layer was washed with water, dried ($MgSO_4$), and evaporated. Fractional distillation of the residue afforded *2-dodecyloxyethyl bromide* (56·7 g., 58%), b. p. 132—133°/1 mm. (Found: C, 56·5; H, 9·9; Br, 26·7. $C_{14}H_{29}OBr$ requires C, 57·3; H, 9·95; Br, 27·25%). d_4^{20} 1·0418, n_D^{20} 1·4576, $[R_L]_D$ 76·75 (calc. 76·52).

p-(ω-Alkoxyalkyl)phenyl Cyanides.—The cyanides were prepared from sodium *p*-cyanophenoxide and the appropriate ω-alkoxyalkyl halide by the method described in Part III (*loc. cit.*). In examples involving the use of an alkoxyalkyl chloride, sodium iodide (0·1 mol.) was added and the period of heating was prolonged to 1—3 days. The following substituted *phenyl cyanides* were prepared: p-(2-*methoxyethoxy*)- (72%), colourless plates, m. p. 43·5—44·5° (Found: N, 8·1. $C_{10}H_{11}O_2N$ requires N, 7·9%); p-(2-*ethoxyethoxy*)- (70%), needles, m. p. 29·5—30·5°, b. p. 113—113°/0·5 mm., 161°/6·5 mm., n_D^{20} 1·5209 (Found: N, 7·4. $C_{11}H_{13}O_2N$ requires N, 7·35%); p-(2-*propoxyethoxy*)- (33%), needles, m. p. 23—24°, b. p. 142—143°/0·6 mm., n_D^{20} 1·5132 (Found: N, 6·85. $C_{12}H_{15}O_2N$ requires N, 6·8%), p-(2-*butoxyethoxy*)- (55%), b. p. 150—151°/0·4 mm., n_D^{20} 1·5080 (Found: N, 6·55. $C_{13}H_{17}O_2N$ requires N, 6·4%); p-(2-*amyloxyethoxy*)- (42%), needles, m. p. 30—31°, b. p. 159—162°/0·6 mm., n_D^{20} 1·5057 (Found: N, 6·1. $C_{14}H_{19}O_2N$ requires N, 6·0%); p-(2-*hexyloxyethoxy*)- (73%), needles, m. p. 33·5—34·5°, b. p. 174—175°/1 mm., n_D^{20} 1·5037 (Found: N, 5·9. $C_{15}H_{21}O_2N$ requires N, 5·65%); p-(2-*heptyloxyethoxy*)- (70%), b. p. 171—174°/0·8 mm., n_D^{20} 1·5012 (Found: N, 5·45. $C_{16}H_{23}O_2N$ requires N, 5·35%); p-(2-*octyloxyethoxy*)- (64%), b. p. 186—190°/2 mm., n_D^{20} 1·4991 (Found: N, 5·15. $C_{17}H_{25}O_2N$ requires N, 5·1%); p-(2-*dodecyloxyethoxy*)- (73%), needles (from ethanol), m. p. 40—42° (Found: N, 4·4. $C_{21}H_{33}O_2N$ requires N, 4·25%); p-(3-*ethoxypropoxy*)- (48%), b. p. 128—129°/0·2 mm., n_D^{20} 1·5155 (Found: N, 7·25. $C_{12}H_{15}O_2N$ requires N, 6·8%).

p-(2-*Hydroxyethoxy*)*phenyl Cyanide.*—Ethylene bromohydrin was boiled under reflux in ethanol for 16 hours with an equivalent of sodium *p*-cyanophenoxide; the solvent was evaporated and the residue was stirred with water and ethyl acetate. Unchanged *p*-cyanophenol was removed from the ethyl acetate solution by N-sodium hydroxide and, after removal of the solvent, the product was crystallised from benzene (yield 61%; m. p. 86·5—87·5°) (Found: N, 8·7. Calc. for $C_9H_9O_2N$: N, 8·6%). Boyd and Marie (*J.*, 1914, **105**, 2138) record m. p. 86°.

p-(2-*Phenoxyethoxy*)*phenyl Cyanide.*—Equimolecular quantities of 2-phenoxyethyl bromide and sodium *p*-cyanophenoxide were boiled together for 16 hours in ethanol; the *product* which separated on addition of water crystallised from light petroleum (b. p. 100—120°) in colourless leaflets (70%), m. p. 112—113° (Found: N, 5·9. $C_{15}H_{13}O_2N$ requires N, 5·9%).

p-(3-*Phenoxypropoxy*)*phenyl cyanide*, obtained in a similar manner to the foregoing compound, crystallised from light petroleum (b. p. 100—120°) as leaflets (79%), m. p. 72—73° (Found: N, 5·6. $C_{16}H_{15}O_2N$ requires N, 5·6%).

p-(*Substituted-alkoxy*)-N-*arylbenzamidines.*—The *p*-(substituted-alkoxy)-*N*-arylbenzamidines described in the table were prepared by heating the appropriate *p*-(substituted-alkoxy)phenyl cyanide with one equivalent of an arylammonium benzenesulphonate at 210° for 1—2 hours (Oxley and Short, *loc. cit.*). The experiments were conducted on a 0·04-g.-mol. scale. A solution of the product in ethanol was treated with aqueous ammonia to liberate the amidine which was purified as the free base, usually after separation from non-basic material as the lactate. Except where otherwise indicated in the footnotes, the amidines were crystallised from light petroleum (b. p. 100—120°). The picrates were prepared by double decomposition of solutions of the amidinium lactates and sodium picrate.

p-(2-*Hydroxyethoxy*)*benzamidine.*—The crude imino-ether hydrochloride, obtained by saturating with dry hydrogen chloride a solution of *p*-(2-hydroxyethoxy)phenyl cyanide (16·3 g.) in dry ethanol (40 c.c.) and keeping 10 days, was shaken for 3 days with saturated ethanolic ammonia (180 c.c.). The *hydrochloride* which separated crystallised as prisms (from dilute hydrochloric acid), m. p. 236—238° (decomp.) (13 g.) (Found: N, 12·7. $C_9H_{13}O_2N_2Cl$ requires N, 12·9%). The *base* (2·9 g.), obtained from the mother-liquors, had m. p. 177—178° (decomp.) (Found: N, 15·3. $C_9H_{12}O_2N_2$ requires N, 15·55%).

p-(2-*Ethoxyethoxy*)*benzamidine.*—A mixture of *p*-(2-ethoxyethoxy)phenyl cyanide (9·6 g.) and dry ethanol (3 c.c.) was treated with dry hydrogen chloride (4·3 g.). The crude imino-ether hydrochloride which separated after 5 days was shaken with saturated ethanolic ammonia (35 c.c.) for 6 days. On being worked up in the usual way, the *amidinium chloride* was obtained as colourless needles which crystallised very slowly from *iso*propanol with solvent of crystallisation and had m. p. 74—76° (4·65 g., 38%) (Found, on material dried at 20°: N, 11·35; Cl^-, 14·35. $C_{11}H_{17}O_2N_2Cl$ requires N, 11·45; Cl, 14·5%). The *picrate* (3·1 g., 14%), obtained from the mother-liquors, crystallised as needles from aqueous ethanol; it melted at 95—96° with effervescence, resolidified, and melted again at 149—151° (Found: loss at 20°/vac., 6·0. Found, on dried material: N, 15·95. $C_{17}H_{19}O_9N_5,1\frac{1}{2}H_2O$ requires H_2O, 5·8%. $C_{17}H_{19}O_9N_5$ requires N, 16·0%). The *benzoate*, plates (from water), had m. p. 204·5—205° (Found: N, 8·4. $C_{16}H_{16}O_2N_2$ requires N, 8·5%).

p-(2-*Ethoxyethoxy*)-N-*cyclohexylbenzamidine.*—To *p*-(2-ethoxyethoxy)phenyl cyanide (7·65 g.) and cyclohexylamine (4 g., 1 mol.), finely powdered aluminium chloride (5·3 g., 1 mol.) was added portionwise and the mixture was heated at 180° for 10 minutes. Basic material was extracted as the lactate from the precipitate obtained on the addition of sodium hydroxide to an aqueous solution of the melt. p-(2-

Ethoxyethoxy)-*N*-*cyclohexylbenzamidine* (4·45 g., 38%), liberated from the lactate, crystallised as colourless plates, m. p. 79—80°, from light petroleum (b. p. 80—100°) (Found: N, 9·85. $C_{17}H_{25}O_2N_3$ requires N, 9·65%). The *picrate* crystallised as short yellow needles from aqueous acetone and had m. p. 60—62° (Found: N, 13·45. $C_{23}H_{28}O_9N_6$ requires N, 13·5%).

p-(2-*Ethoxyethoxy*)-*N*-2′-*pyridylbenzamidine* was prepared in a similar manner to the foregoing compound from equimolecular quantities of *p*-(2-ethoxyethoxy)phenyl cyanide, 2-aminopyridine, and aluminium chloride in 36% yield; it crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 101—102° (Found: N, 14·95. $C_{16}H_{19}O_2N_3$ requires N, 14·75%). The *monopicrate*, long yellow needles from aqueous ethanol, had m. p. 183—184° (Found: N, 16·35; $C_6H_2O_7N_3$, 44·4. $C_{16}H_{19}O_2N_3,C_6H_3O_7N_3$ requires N, 16·35; $C_6H_2O_7N_3$, 44·5%).

p-(2-*Ethoxyethoxy*)-*N*-*benzylbenzamidine*.—(i) *p*-(2-Ethoxyethoxy)phenyl cyanide (9·55 g.), benzylamine (5·35 g., 1 mol.), and aluminium chloride (6·7 g., 1 mol.) were brought into reaction in the usual way at 180° for 30 minutes. Basic material, liberated from an aqueous solution of the melt by sodium hydroxide, was collected in chloroform, recovered, purified *via* the lactate, again liberated, collected in chloroform, and recovered. *p*-(2-*Ethoxyethoxy*)-*N*-*benzylbenzamidine* slowly crystallised from a solution of the residue in light petroleum (b. p. 100—120°) as plates (3·6 g., 24%), m. p. 80·5—81° (Found: N, 9·5. $C_{18}H_{22}O_2N_2$ requires N, 9·4%). The *picrate*, m. p. 56—58°, was obtained as clusters of yellow needles from aqueous ethanol (Found: loss at 20°/vac., 2·0. Found, on dried material: N, 13·4. $C_{24}H_{25}O_9N_5,\frac{1}{2}H_2O$ requires H_2O, 1·7%. $C_{24}H_{25}O_9N_5$ requires N, 13·3%).

(ii) A mixture of *p*-(2-ethoxyethoxy)phenyl cyanide (9·6 g.) and benzylammonium thiocyanate (8·3 g., 1 mol.), heated at 180° for 105 minutes, afforded, on being worked up in the usual way (Partridge and Short, *loc. cit.*), the amidinium picrate (0·8 g., 3%), m. p. and mixed m. p. 56—58°.

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Research Laboratories, Boots Pure Drug Co. Ltd.,
Nottingham.
University of Nottingham.

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92. *Some* meso-*Amino-acridines and -quinolines derived from 2-Aminodiphenyl.*

By J. H. Wilkinson.

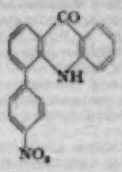
Several new derivatives of 5-aminoacridine and 4-aminoquinoline have been prepared in order to study their effects on mitosis and tissue respiration. Difficulty was experienced in the preparation of 5-*amino*-1-*p*-*nitrophenylacridine*; the reaction of 1-*p*-*nitrophenylacridone* with phosphorus oxychloride is discussed.

The observations of Dustin (*Arch. Exp. Zellforsch.*, 1939, **22**, 395; *Sang*, 1937, **12**, 677) and Bucher (*Z. Zellforsch.*, 1939, **29**, 283) that trypaflavine (acriflavine) possessed a powerful inhibitory effect on mitosis suggested that it might be profitable to study certain other acridine derivatives from this viewpoint. A preliminary report (Lasnitzki and Wilkinson, *Brit. J. Cancer*, 1948, **2**, 369) showed that several other compounds of this type inhibited mitosis in tissue cultures of chick-embryo fibroblasts, and that it would be desirable to extend the study. Recently a number of quaternary salts of heterocyclic compounds has been prepared by Hartwell and Kornberg (*J. Amer. Chem. Soc.*, 1945, **67**, 1606; 1946, **68**, 868, 1131) and some have shown activity against tumour cells (Peters, "Approaches to Tumor Chemotherapy," 1947, p. 244). In the present work therefore, the emphasis was originally placed on the preparation of quaternary salts, but the biological results (Lasnitzki and Wilkinson, *loc. cit.*) have indicated that, with acridine derivatives, quaternisation was not an essential pre-requisite for anti-mitotic activity (contrast O'Connor, *Nature*, 1949, **163**, 408; *Brit. J. Exp. Path.*, 1949, **30**, 30). Several new derivatives of 5-aminoacridine have therefore been prepared with the object of examining their effects on cell division and respiration. Similar 4-aminoquinolines have also been prepared for comparison. The biological results will be published elsewhere.

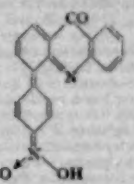
The 5-aminoacridines were prepared by standard methods from the appropriately substituted anilines which were condensed with *o*-chloro- or 2 : 4-dichloro-benzoic acid to give the corresponding diphenylamine-2-carboxylic acids. 4 : 4′-Dinitro-2-aminodiphenyl, however, failed to react under any of the conditions tried, whilst 4′-nitro-2-aminodiphenyl reacted normally to give 2′-*p*-*nitrophenyldiphenylamine-2-carboxylic acid*. The acids were cyclised with phosphorus oxychloride to give the corresponding 5-chloroacridines, but the 1-*p*-nitrophenyl derivative proved so sensitive to hydrolysis that it could be obtained only in minute amounts, the bulk being isolated as 1-*p*-*nitrophenylacridone*. Interaction with ammonium carbonate in molten phenol

by the method of Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169r) gave 5-amino-1-phenylacridine, *9-chloro-5-amino-1-phenylacridine*, and *5-amino-1-p-nitrophenylacridine*.

p-Nitrophenylacridone (I) proved highly resistant to phosphorus oxychloride, possibly because of the effect of the nitro-group on the ratio of the contributing resonance forms (cf.



(I.)



(II.)

Hunter, *J.*, 1945, 806). Thus it is probable that the compound exists largely as the "*ψ*-nitrolic acid" (II), a suggestion supported by the red colour of a solution in alcoholic sodium hydroxide. If this assumption is correct, the proton will not be available for the formation of the 5-hydroxyacridine structure presumably necessary for the promotion of reaction with phosphorus oxychloride. It must be assumed that the effect of the nitro-group is accentuated by transmission through the phenyl group, for 1-nitroacridone, though it does not react under normal conditions with phosphorus oxychloride, undergoes chlorination with phosphorus pentachloride in a high-boiling solvent (Albert and Gledhill, *loc. cit.*; cf. Hampton and Magrath, *J.*, 1949, 1008). *p*-Nitrophenylacridone failed to react with phosphorus pentachloride in xylene.

Since the principal object in preparing 5-amino-1-*p*-nitrophenylacridine was to reduce it to the corresponding diamino-compound, the very poor yields obtained led to the study of alternative methods. *2'-p-Aminophenyldiphenylamine-2-carboxylic acid* and *1-p-aminophenylacridone* were obtained by reduction of the respective nitro-compounds with stannous chloride, but neither reacted satisfactorily with phosphorus oxychloride.

The quinoline derivatives were prepared by condensing various 2-aminodiphenyls with ethoxymethylenemalonic ester (Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890; Price and Roberts, *ibid.*, 1946, **68**, 1204; Duffin and Kendall, *J.*, 1948, 893). In most cases the required ethyl 4-hydroxyquinoline-3-carboxylate was obtained, but when 4 : 4'-dinitro-2-aminodiphenyl was used ring closure did not occur and *ethyl 4' : 5-dinitro-2-phenylaniline-methylenemalonate* was isolated: several cyclising agents were tried without success. Hydrolysis and decarboxylation gave the 4-hydroxyquinolines which were converted into the 4-chloroquinolines by phosphorus oxychloride. Subsequent treatment with ammonium carbonate in phenol at 180° gave the required 4-aminoquinolines.

An attempt was made to prepare the quaternary 1-methyl derivatives of *4-amino-8-phenylan 1-8-p-nitrophenyl-quinoline* by the methods used for the acridine compounds, but this succeeded only in the latter case. The *product* was reduced to the corresponding 4 : 4'-diamino-compound (isolated as its *bromide hydrobromide*).

When *4-acetamido-8-phenylquinoline* was heated with methyl sulphate in nitrobenzene solution and the product hydrolysed with hydrobromic acid, an uncrystallisable oil was obtained. However with methyl toluene-*p*-sulphonate in the absence of a solvent it gave *4-acetamido-8-phenyl-1-methylquinolinium toluene-p-sulphonate*. Removal of the acetyl group proved difficult, for the compound was recovered unchanged after being heated with 2N-sulphuric acid or -hydrobromic acid at 90° for 2 hours. Boiling with 4N-hydrobromic acid, however, not only deacetylated, but also deaminated, the product.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

5-Chloro-2'-phenyldiphenylamine-2-carboxylic Acid.—A solution of 2 : 4-dichlorobenzoic acid (9·55 g.) in amyl alcohol (40 c.c.) was treated with anhydrous potassium carbonate (7 g.). 2-Aminodiphenyl (8·45 g.) and copper (0·1 g.) were added, and the mixture was refluxed for 6 hours. The amyl alcohol was removed by steam-distillation, and the residue filtered. The ammonium salt of the product was precipitated by the addition of 30% ammonium chloride solution (50 c.c.). This salt was collected and dissolved in 2N-potassium hydroxide, and the free *acid* (8·2 g., 51%) liberated with 2N-hydrochloric acid. It crystallised from toluene in pale yellow prisms, m. p. 203° (Found: C, 70·7; H, 4·3; N, 4·3; Cl, 11·0. $C_{19}H_{14}O_2NCl$ requires C, 70·7; H, 4·3; N, 4·3; Cl, 11·0%).

5 : 9-Dichloro-1-phenylacridine.—The foregoing acid (2 g.) was refluxed with phosphorus oxychloride (5 c.c.) for 1 hour. Excess of the reagent was removed under reduced pressure, and the residue dissolved in chloroform (30 c.c.). The solution was stirred for 30 minutes with ammonia solution (*d* 0·88; 30 c.c.),

cooled with ice. The chloroform layer was separated and the solvent removed. The *product* (2 g.) crystallised from anhydrous benzene in bright yellow needles, m. p. 164° (Found: N, 4·6; Cl, 21·4. $C_{19}H_{11}NCl_2$ requires N, 4·3; Cl, 21·9%).

9-Chloro-5-amino-1-phenylacridine.—5 : 9-Dichloro-1-phenylacridine (5 g.) was dissolved in phenol (15 g.) at 80°, and ammonium carbonate (1·5 g.) added. The temperature was raised to 140° for 1 hour. Acetone (70 c.c.) was added to the cooled melt, and the precipitated *9-chloro-5-amino-1-phenylacridine hydrochloride* (3·76 g., 71%) collected. It crystallised from 20% alcohol in bright yellow prisms, m. p. over 300°, sparingly soluble in water (Found: N, 7·25; Cl, 18·3. $C_{19}H_{12}N_2Cl,HCl,\frac{3}{2}H_2O$ requires N, 7·1; Cl, 18·0%). The *base* was obtained in yellow prisms from chlorobenzene, m. p. 189° (Found: C, 74·4; H, 4·25; N, 8·9. $C_{19}H_{12}N_2Cl$ requires C, 74·8; H, 4·25; N, 9·2%).

The *acetamido*-compound (0·94 g., 82%) was obtained by heating the amino-compound (1 g.) with acetic anhydride (4 c.c.) and acetic acid (2 c.c.) at 105° for 30 minutes, and treating the cooled mixture with benzene (20 c.c.). It crystallised from dioxan in fine pale yellow needles, m. p. 309° (Found: N, 8·35. $C_{21}H_{15}ON_2Cl$ requires N, 8·1%).

9-Chloro-5-amino-1-phenyl-10-methylacridinium bromide. The above acetyl derivative (0·7 g.) was treated with methyl sulphate (0·7 c.c.) in nitrobenzene (7 c.c.) at 140—150° for 1 hour. After treatment with benzene (15 c.c.) overnight, the precipitate was collected and hydrolysed by heating it with 48% hydrobromic acid (5 c.c.) on a water-bath for 1 hour. The *product* (0·6 g., 74%) crystallised from water in bright yellow prisms, m. p. over 300° (Found: N, 7·25. $C_{20}H_{14}N_2ClBr$ requires N, 7·0%).

2′-p-Nitrophenyldiphenylamine-2-carboxylic Acid.—o-Chlorobenzoic acid (1·56 g.) was dissolved in amyl alcohol (3 c.c.), and the solution treated with potassium carbonate (1·4 g.). 4′-Nitro-2-amino-diphenyl (1·91 g.) and copper (0·1 g.) were added, and the mixture was refluxed for 6 hours. The solvent was removed by steam-distillation and the residue filtered. The filtrate was acidified with acetic acid to precipitate the required *acid* (2·45 g., 81%), which crystallised from 70% alcohol in bright orange-yellow needles, m. p. 243°, sparingly soluble in most organic solvents (Found: C, 68·6; H, 4·3; N, 8·7. $C_{19}H_{14}O_4N_2$ requires C, 68·3; H, 4·2; N, 8·4%).

5-Amino-1-p-nitrophenylacridine.—*2′-p*-Nitrophenyldiphenylamine-2-carboxylic acid (0·7 g.) was treated with phosphorus oxychloride (2 c.c.) as described for *5* : 9-dichloro-1-phenylacridine. The resultant crude 5-chloro-1-*p*-nitrophenylacridine proved very susceptible to hydrolysis during isolation and it was considered advisable to attempt the conversion of this material into the corresponding 5-amino-compound without further purification. 1-p-*Nitrophenylacridone* (0·45 g.) was obtained as a by-product; this crystallised from pyridine in small pale yellow needles, m. p. 263—263° (Found: N, 8·75. $C_{19}H_{12}O_3N_2$ requires N, 8·9%). The crude 5-chloroacridine (0·25 g.) was dissolved in phenol (1 g.) at 70° and treated with ammonium carbonate (0·1 g.) at 120° for 1 hour. Acetone (10 c.c.) was added to precipitate the yellow hydrochloride, which was sparingly soluble in cold water and underwent rapid hydrolysis to the acridone when an aqueous suspension was heated. The base was obtained by suspending the hydrochloride in 90% alcohol and stirring at 20° with a small excess of 2*N*-sodium hydroxide. After 1 hour this was collected by filtration and crystallised from chlorobenzene. *5-Amino-1-p-nitrophenylacridine* (90 mg.) was obtained as red needles, m. p. 277—278° (Found: C, 71·5; H, 4·3; N, 13·0. $C_{19}H_{13}O_2N_3$ requires C, 72·3; H, 4·15; N, 13·3%).

1-p-*Aminophenylacridone.*—1-*p*-Nitrophenylacridone (3·16 g.) was finely powdered and heated on a water-bath with stannous chloride (6·8 g.) and hydrochloric acid (50 c.c.) for 2 hours. The mixture was set aside overnight and the solid collected. It was triturated several times with *5N*-sodium hydroxide and washed with water. 1-p-*Aminophenylacridone* was thus obtained as a red powder which crystallised from pyridine in irregular orange crystals, m. p. over 300° (Found: N, 9·5. $C_{19}H_{14}ON_2$ requires N, 9·8%).

2′-p-Aminophenyldiphenylamine-2-carboxylic Acid.—*2′-p*-Nitrophenyldiphenylamine-2-carboxylic acid (2·75 g.) was heated under reflux with stannous chloride (6 g.) in alcohol (25 c.c.) and hydrochloric acid (*d* 1·16; 15 c.c.) for 3 hours. During this period the solid slowly dissolved. The alcohol was removed by distillation, and the cooled residue treated with saturated sodium acetate solution (100 c.c.). The solid was collected, washed with water, and drained as completely as possible. It was then extracted with three 100 c.c. portions of boiling alcohol. The solvent was removed and the residue dissolved in *N*/2-sodium hydroxide. Acidification with acetic acid gave *2′-p-aminophenyldiphenylamine-2-carboxylic acid* which crystallised from 90% alcohol in buff-coloured hexagonal plates, m. p. 188—189° (Found: C, 74·7; H, 5·35; N, 8·9. $C_{19}H_{16}O_2N_2$ requires C, 74·6; H, 5·25; N, 9·2%).

5-2′-Phenylethylaminoacridine.—5-Chloroacridine (10·67 g.) was dissolved in phenol (30 g.) at 70°; 2-phenylethylamine (6·1 g.) was added, and the mixture heated at 120° for 1 hour. A green gum was precipitated from the cooled melt by treatment with ether (100 c.c.). When kept, this hardened to a yellow solid which was washed with ether and crystallised twice from methanol. *5-2′-Phenylethylamino-acridine hydrochloride* (11·7 g., 70%) was thus obtained as lemon-yellow rectangular prisms, m. p. 214—215°, sparingly soluble in water but readily soluble in alcohol (Found: N, 8·1; Cl, 10·9. $C_{21}H_{18}N_2,HCl$ requires N, 8·4; Cl, 10·6%). The *base* was obtained as an oil which crystallised, on treatment with benzene and light petroleum (b. p. 40—60°), in bright yellow irregular crystals, m. p. 79—80°, highly soluble in most organic solvents (Found: C, 84·6; H, 6·25; N, 9·1. $C_{21}H_{18}N_2$ requires C, 84·6; H, 6·0; N, 9·4%). The *acetyl* derivative separated from alcohol in colourless needles, m. p. 230° (Found: N, 8·3. $C_{23}H_{20}ON_2$ requires N, 8·2%).

Quinoline Derivatives.—*Ethyl 4-hydroxy-8-phenylquinoline-3-carboxylate.* 2-Aminodiphenyl (16·9 g.) and ethoxymethylenemalonic ester (21·6 g.) were dissolved in "Dowtherm" (70 c.c.). The temperature of the solution was gradually raised to 270°, and the alcohol eliminated during the reaction collected (10·3 c.c. Theor.: 11·5 c.c.). The *ester* (23·5 g., 80%) which separated from the cooled mixture was collected by filtration and washed successively with benzene and light petroleum (b. p. 40—60°). It crystallised from alcohol in colourless needles, m. p. 249° (Found: C, 73·7; H, 5·5; N, 4·85. $C_{19}H_{15}O_3N$ requires C, 73·7; H, 5·1; N, 4·8%).

4-Hydroxy-8-phenylquinoline-3-carboxylic acid. The ethyl ester (20 g.) was heated under reflux with 8*N*-sodium hydroxide (100 c.c.) for 1½ hours, whereby complete dissolution was obtained. After cooling,

the mixture was filtered, diluted with water (200 c.c.), and acidified with hydrochloric acid, to precipitate the *acid* (18 g.), colourless rhombs (from methyl ethyl ketone), m. p. 241—242°, sparingly soluble in alcohol (Found: C, 72·3; H, 4·3; N, 5·15. $C_{16}H_{11}O_3N$ requires C, 72·4; H, 4·2; N, 5·3%).

4-Hydroxy-3-phenylquinoline. The above acid (10·2 g.) was added during 15 minutes to "Dowtherm" (80 c.c.) maintained at 250° during the addition and for a further 30 minutes. The *base* (13·5 g.) which separated on cooling was collected and washed with light petroleum (b. p. 40—60°); it crystallised from 70% alcohol in colourless plates, m. p. 201° (Found: C, 81·6; H, 5·0; N, 6·5. $C_{15}H_{11}ON$ requires C, 81·4; H, 5·0; N, 6·35%).

4-Chloro-3-phenylquinoline. 4-Hydroxy-3-phenylquinoline (2·2 g.) was heated under reflux for 2 hours with phosphorus oxychloride (6 c.c.). The cooled solution was poured on crushed ice (30 g.) and made alkaline with aqueous ammonia. The gum which separated hardened to a white solid (2·27 g., 95%) on trituration with dilute aqueous ammonia. It was collected by filtration and dried over calcium chloride. *4-Chloro-3-phenylquinoline* crystallised from alcohol in colourless needles, m. p. 93° (Found: C, 75·1; H, 4·1; N, 5·65; Cl, 15·0. $C_{15}H_{10}NCl$ requires C, 75·1; H, 4·2; N, 5·85; Cl, 14·85%).

4-Amino-3-phenylquinoline. 4-Chloro-3-phenylquinoline (2 g.) was dissolved in phenol (6 g.) at 70° and treated with powdered ammonium carbonate (1 g.). The temperature was raised to 160° for 2 hours. After cooling, the hydrochloride of the product was precipitated with acetone (50 c.c.) and converted into the *base* (1·1 g.) with aqueous sodium hydroxide. It crystallised from toluene in colourless prisms, m. p. 166° (Found: C, 81·8; H, 5·45; N, 12·8. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·45; N, 12·7%). The *acetyl* derivative separated from alcohol in colourless cubes, m. p. 206—207° (Found: C, 77·6; H, 5·45; N, 10·9. $C_{17}H_{14}ON_2$ requires C, 77·9; H, 5·35; N, 10·7%).

4-Acetamido-3-phenyl-1-methylquinolinium toluene-p-sulphonate. A mixture of 4-acetamido-3-phenylquinoline (1 g.) and methyl toluene-*p*-sulphonate (1 g.) was heated at 160° for 30 minutes. The cooled melt was crushed and triturated with hot benzene. The residual *salt* crystallised from water or alcohol in colourless needles, m. p. 254—255° (Found: C, 67·1; H, 5·4; N, 6·3; S, 7·1. $C_{25}H_{24}O_4N_2S$ requires C, 67·0; H, 5·36; N, 6·3; S, 7·1%).

Attempted Hydrolysis of 4-Acetamido-3-phenyl-1-methylquinolinium toluene-p-sulphonate. (i) The quaternary salt (0·32 g.) was heated on a steam-bath with 2*N*-sulphuric acid (3 c.c.) for 1 hour. The solid (0·21 g.) which separated on cooling had m. p. 254° and proved to be unchanged starting material (Found: N, 6·5; S, 7·4%). (ii) Similar treatment with 2*N*-hydrobromic acid also failed to hydrolyse the toluene-*p*-sulphonate. (iii) 0·5 G. of the salt was heated under reflux with 4*N*-hydrobromic acid (5 c.c.) for 2 hours. The oil which separated on cooling soon hardened to a solid, which was dissolved in hot water. The resulting solution was made alkaline with sodium hydroxide, and the precipitate produced was dissolved in hot 2*N*-hydrobromic acid. After two recrystallisations from water, the solid which separated on cooling, was obtained in colourless prisms, m. p. 155—156°. It contained no bromine, was devoid of basic properties, and evidently consisted of *4-hydroxy-2-keto-3-phenyl-1-methyl-1:2-dihydroquinoline* or its tautomer (Found: C, 76·1; H, 6·1; N, 5·9. $C_{16}H_{15}O_2N$ requires C, 76·2; H, 5·95; N, 5·55%).

Ethyl 4-hydroxy-3-p-nitrophenylquinoline-3-carboxylate. 4'-Nitro-2-aminodiphenyl (10·7 g.) and ethoxymethylenemalonic ester (10·8 g.) were heated in "Dowtherm" (40 c.c.) as described above. The theoretical amount of alcohol was eliminated after 2 hours. The product (13·9 g., 82%), which crystallised, was washed with benzene and light petroleum (b. p. 40—60°). The *ester* was sparingly soluble in most organic solvents, and separated from aqueous pyridine in pale yellow masses, m. p. 285° (Found: C, 63·7; H, 4·2; N, 8·5. $C_{18}H_{14}O_5N_2$ requires C, 63·9; H, 4·15; N, 8·3%).

4-Hydroxy-3-p-nitrophenylquinoline. The ester (13 g.) was hydrolysed by being heated under reflux with 2*N*-sodium hydroxide (200 c.c.) for 1 hour. The resulting solution was filtered while still hot, and the quinoline-3-carboxylic acid (12 g.) precipitated with hydrochloric acid. It was obtained as a pale yellow powder, m. p. 280° (decomp.), very sparingly soluble in organic solvents. No suitable solvent for crystallisation was found. The acid (12 g.) was gradually added to boiling "Dowtherm" (60 c.c.), and the mixture maintained at 250—260° for 1 hour and then cooled. The product (9·85 g., 95%) was collected, washed with benzene and light petroleum (b. p. 40—60°), and dried at 100°. It crystallised from 70% aqueous pyridine in yellow irregular prisms, m. p. >300°, sparingly soluble in most organic solvents (Found: N, 10·7. $C_{15}H_{10}O_3N_2$ requires N, 10·4%).

4-Chloro-3-p-nitrophenylquinoline. 4-Hydroxy-3-*p*-nitrophenylquinoline (9·5 g.) was refluxed with phosphorus oxychloride (20 c.c.) for 2 hours. The mixture was cooled, poured on crushed ice, and neutralised with aqueous ammonia. The solid *base* (10·15 g., 100%) crystallised from 80% aqueous dioxan in fine pale yellow needles, m. p. 224° (Found: N, 9·6. $C_{15}H_9O_2N_2Cl$ requires N, 9·75%).

4-Amino-3-p-nitrophenylquinoline. 4-Chloro-3-*p*-nitrophenylquinoline (9·7 g.) was dissolved in phenol (27 g.) at 100°, and ammonium carbonate (4 g.) was added portionwise whilst the temperature was raised to 180° for 2 hours. The product (5·8 g., 65%) was isolated in the same manner as 4-amino-3-phenylquinoline. *4-Amino-3-p-nitrophenylquinoline* crystallised from alcohol in lemon-yellow, squat prisms, m. p. 224—225° (Found: C, 67·6; H, 4·15; N, 16·0. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·15; N, 15·8%). The *acetyl* derivative crystallised from alcohol in pale yellow needles, m. p. 242° (Found: N, 13·8. $C_{17}H_{13}O_3N_3$ requires N, 13·65%).

4-Amino-3-p-nitrophenyl-1-methylquinolinium bromide. 4-Acetamido-3-*p*-nitrophenylquinoline (1·9 g.) was dissolved in nitrobenzene (7 c.c.) and treated with methyl sulphate (2 c.c.) at 150° for 1 hour. The cooled mixture was treated with benzene (25 c.c.) and set aside for 4 hours. The gum was washed by decantation with benzene and hydrolysed with 48% hydrobromic acid (10 c.c.) on a steam-bath for 1 hour. The product (1·9 g., 85%) was collected and washed with water. *4-Amino-3-p-nitrophenyl-1-methylquinolinium bromide* crystallised from water in pale yellow plates, m. p. 279—281° (decomp.) (Found: N, 11·6. $C_{16}H_{14}O_2N_3Br$ requires N, 11·7%). An aqueous solution gave no precipitate with saturated sodium hydrogen carbonate solution, but sodium hydroxide precipitated the yellow *pseudo*-base.

4:4'-Diamino-3-phenyl-1-methylquinolinium bromide hydrobromide. The nitro-salt (1·5 g.) was suspended in 4*N*-hydrochloric acid (8 c.c.) and treated with stannous chloride (3 g.) under reflux for 3 hours. The cooled mixture was diluted with water (30 c.c.) and made alkaline to phenolphthalein with

5N-sodium hydroxide. The solid base was collected and washed with water. It was dissolved in hot 2N-hydrobromic acid (20 c.c.) and, on cooling, the required *bromide hydrobromide* (1·29 g., 94%) separated. It crystallised from water in buff-coloured needles, m. p. >300°, charring at *ca.* 295° (Found: N, 9·0; Br, 34·8. $C_{13}H_{11}N_2Br,HBr,3H_2O$ requires N, 9·0; Br, 34·4%).

Attempted Preparation of 4′: 5-Dinitro-4-hydroxy-8-phenylquinoline.—4 : 4′-Dinitro-2-aminodiphenyl (12·95 g.) and ethoxymethylenemalonic ester (10·8 g.) were heated with "Dowtherm" (50 c.c.) at 250° for 4 hours, after which no more alcohol distilled off. Only half of the theoretical amount was obtained. On cooling, *ethyl 4′: 5-dinitro-2-phenylanilinomethylenemalonate* (12·1 g., 56%) separated. This crystallised from alcohol in bright yellow needles, m. p. 188°, sparingly soluble in most organic solvents, but readily soluble in dioxan and *p*-tolyl methyl ether (Found: C, 55·8; H, 4·55; N, 9·8. $C_{20}H_{19}O_6N_3$ requires C, 55·9; H, 4·45; N, 9·75%). Several methods of cyclisation including heating with sulphuric and phosphoric acids were attempted, but in no case was the required ethyl 4′: 5-dinitro-8-phenyl-4-quinolone-3-carboxylate obtained.

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Department of Chemical Pathology,
Westminster Medical School (University of London),
17, Horseferry Road, London, S.W.1. [*Received, November 22nd,* 1949.]

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93. *The Structure of Molecular Compounds. Part IX. A Compound of Xenon and Quinol.*

By H. M. Powell.

The preparation of the compound of composition $3C_6H_4(OH)_2{\cdot}0{\cdot}88Xe$ is described. The compound, similar in properties and structure to the corresponding argon and krypton compounds, contains 26% of xenon.

In Parts VII and VIII (*J.*, 1950, 298, 300) the preparation of compounds of quinol with argon and with krypton was described, and from consideration of the sizes of inert-gas atoms, which in these compounds are enclosed in a cage structure formed by hydrogen-bonded quinol molecules, it seemed probable that xenon would also fit into the cavity and thus form a similar compound.

The preparation was carried out in the manner previously described (Part VII) by cooling an aqueous solution of quinol in a pressure-vessel containing xenon. With the material available the highest pressure obtainable was 14 atmospheres. In these conditions the product obtained in the first experiment contained xenon but did not, as in the case of the argon and krypton compounds, contain large crystals suitable for separation by sieving or hand picking from any α-quinol present. From the loss of weight on heating it was found to have about one-third of the xenon content expected for the formula $3C_6H_4(OH)_2Xe$. The product was not homogeneous and contained a small proportion of material of density greater than that of carbon tetrachloride but the bulk of it had a lower density. A second preparation gave 2 g. of product from which a few stumpy crystals of about 1 mm. diameter were separated by hand. Most of the product was then thrown into carbon tetrachloride and the main portion removed by flotation. About 0·1 g. of a dense fraction that sank in carbon tetrachloride was separated, and the xenon content determined. This part contained 26% of xenon [$3C_6H_4(OH)_2Xe$ requires Xe, 28·5%]. The composition of the analysed sample may be represented as $3C_6H_4(OH)_2{\cdot}0{\cdot}88Xe$, *i.e.*, 88% of the available cavities contain a xenon atom. The density of the hand-picked crystals was determined by flotation in mixtures of carbon tetrachloride and ethylene dibromide. The highest value observed was 1·69 g./c.c. The density calculated for the xenon compound, on the assumptions that it has the same unit cell dimensions as the argon compound and that all the cavities are occupied, is 1·77 g./c.c. The observed value corresponds to a composition $3C_6H_4(OH)_2{\cdot}0{\cdot}84Xe$. The high density readily distinguishes the substance from the quinol compounds of argon or krypton, which have calculated maximum values of 1·42 and 1·59 g./c.c., respectively, and as prepared have somewhat lower values than those calculated.

The crystals are colourless and show no signs of decomposition after several days. On dissolution they liberate xenon, and, on heating, quinol volatilises and thus sets free xenon. A preliminary *X*-ray examination shows that they have a unit cell similar to those of the argon and krypton compounds.

The less dense fraction of the yield removed by flotation with carbon tetrachloride contained 10% of xenon. It may be a mixture but has not been examined in detail.

The author expresses his thanks to the British Oxygen Co., who prepared a suitable cylinder of xenon for this work.

LABORATORY OF CHEMICAL CRYSTALLOGRAPHY,
UNIVERSITY MUSEUM, OXFORD.

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94. o-*Mercapto-azo-compounds. Part I. The Coupling of Tetrazotised* 2 : 2′-*Diaminodiphenyl Disulphide with* β-*Naphthol.*

By A. BURAWOY and C. TURNER.

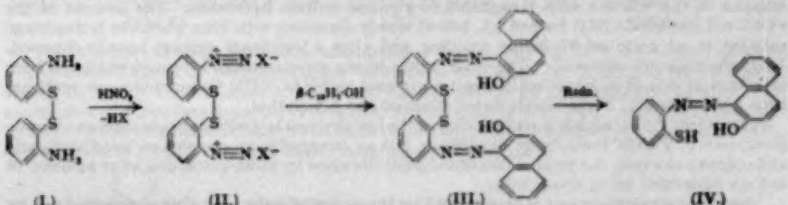
A general method for the preparation of the hitherto unknown *o*-mercapto-azo-compounds is developed.

Only monodiazotisation of 2 : 2′-diaminodiphenyl disulphide occurs in dilute acid, the product decomposing spontaneously to yield benz-1-thia-2 : 3-diazole (V). The tetrazonium salt (II) is formed and is stable in concentrated sulphuric acid, but is also decomposed by water with the formation of benzthiadiazole.

Coupling takes place when the concentrated sulphuric acid solution is added directly to solutions or suspensions of β-naphthol in aqueous sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium acetate, or pyridine. Three different reactions are encountered. In all cases an intermediate product (XXX), formed by coupling with one mole of β-naphthol, is first formed. In sodium hydroxide and carbonate solution this decomposes to benzthiadiazole and unstable *o*-(2-hydroxynaphthalene-1-azo)benzenesulphenic acid (XXXI), which undergoes spontaneous disproportionation in sodium hydroxide solution, to yield di-*o*-(2-hydroxynaphthalene-1-azo)phenyl disulphide (III) and *o*-(2-hydroxynaphthalene-1-azo)benzenesulphinic acid (IX), whereas in sodium carbonate solution condensation with a second mole of β-naphthol to *o*-(2-hydroxynaphthalene-1-azo)phenyl 2-hydroxy-1-naphthyl sulphide (X) takes place. On the other hand, the intermediate (XXX) is sufficiently stable in sodium hydrogen carbonate or acetate solution or in pyridine to allow coupling with a second mole of β-naphthol in preference to degradation, the disulphide (III) being formed in good yield.

The mechanisms of these reactions are confirmed by independent experiments, and the structures of the products are established by unambiguous methods.

OWING to their technical and theoretical importance, *o*-hydroxy-azo-compounds have been the subject of numerous investigations. A study of the properties of the corresponding *o*-mercapto-azo-compounds should also be of interest. Such substances are as yet unknown, partly because the methods normally used in the preparation of the *o*-hydroxy-azo-compounds (reaction of a diazo-compound with a phenol coupling in the *o*-position, and reaction of a diazotised *o*-aminophenol with a suitable coupling component) are not applicable in this series. Thus, thiophenols are unable to couple, forming instead the corresponding diazothio-ethers Ar·N:N·SAr′ which apparently cannot be rearranged to yield azo-compounds (Ziegler, *Ber.*, 1890, **23**, 2471; Stadler, *Ber.*, 1884, **17**, 2076; Hantzsch and Freese, *Ber.*, 1895, **28**, 3237; Dunn and Fletcher, *Trans*



(I.) (II.) (III.) (IV.)

Kansas Acad. Sci., 1934, **37**, 123), and *o*-aminothiophenols yield on diazotisation the non-coupling benz-1-thia-2 : 3-diazoles (cf. Bernthsen, *Annalen*, 1889, **251**, 30; Jacobson *et al.*, *ibid.*, 1893, **277**, 209, 237, 257).

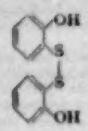
A few *o*-alkylthio-azo-compounds have been prepared, but only 2 : 2′-di(methylthio)azobenzene (Brand, *Ber.*, 1909, **42**, 3463) and 5-nitro-2-methylthiobenzeneazo-β-naphthol (Hodgson and Dodgson, *J.*, 1948, 870) appear to have been obtained in a pure state.

We first considered the possibility of tetrazotising 2 : 2′-diaminodiphenyl disulphide (I), coupling the tetrazonium salt (II) with β-naphthol, and finally reducing the di-*o*-(2-hydroxy-

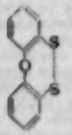
naphthalene-1-azo)phenyl disulphide (III) formed to 1-(*o*-mercaptobenzeneazo)-2-naphthol (IV). Although we have succeeded in our aim, the reactions proved to be very complex.*

Previous attempts to prepare the tetrazonium salt of 2 : 2′-diaminodiphenyl disulphide or to couple it have been unsuccessful. Jacobson (*Ber.*, 1887, **20**, 1902) mentioned that boiling diazotised 2 : 2′-diaminodiphenyl disulphide with water yields the steam-volatile benz-1-thia-2 : 3-diazole (V). Hodgson (*J. Soc. Dyers and Col.*, 1924, **40**, 330) obtained a 50% yield of (V) on diazotising the diamine in dilute mineral acids, no coupling with β-naphthol being observed. Guha and Ghosh (*J. Indian Inst. Sci.*, 1929, **12**, *A*, 31) claimed the isolation of the tetrazonium salt (II), describing it as insoluble in water and unable to react with aniline or potassium ethyl xanthate; they also stated that it decomposed when stored at $> 20°$ or on subjection to the action of reducing agents or of coupling components, with the formation of a brown tar which, on steam-distillation, yielded (VII) by dehydration of di-*o*-hydroxyphenyl disulphide (VI). Not only does this contrast with Jacobson's and Hodgson's earlier observations, but (VI) has already been described by Haitinger (*Monatsh.*, 1883, **4**, 165) as stable up to 200°.

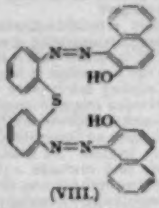
(V.)



(VI.)



(VII.)



(VIII.)

Re-investigating the action of nitrous acid on 2 : 2′-diaminodiphenyl disulphide, we found, in agreement with Hodgson, that in dilute hydrochloric or sulphuric acid benzthiadiazole contaminated with varying amounts of resinous material separates immediately on addition of sodium nitrite, and that it can be isolated in 45—60% yield by ether-extraction. We do not confirm Guha and Ghosh's claims. The supposed tetrazonium salt decomposing above 20° is undoubtedly impure benzthiadiazole which melts at about 24° and solidifies again on cooling. Steam-distillation yields pure benzthiadiazole, but no (VII).

The tetrazonium *salt* (II) is formed when diazotisation is carried out in concentrated sulphuric acid with nitrosylsulphuric acid. It is stable in this medium, but is slowly decomposed by water with the formation of benzthiadiazole. When the sulphuric acid solution is poured into ice-water and the resultant clear solution immediately extracted with ether, only traces of benzthiadiazole are obtained. However, it soon begins to separate and after about three hours can be extracted in about 75% yield. This, incidentally, compares favourably with other known methods of preparation.

The slow degradation of the tetrazonium salt (II) in water is also indicated by coupling samples of the solution with β-naphthol in aqueous sodium hydroxide. The amount of the violet-red disulphide (III) formed (cf. below) slowly decreases with time when the tetrazonium solution is set aside (at 0°) before coupling, and after a few hours' storage none is obtained. In its place a small amount ($< 5\%$) of an orange-brown azo-compound is formed which has been identified as *di*-*o*-(*2-hydroxynaphthalene-1-azo)phenyl sulphide* (VIII) by unambiguous synthesis from tetrazotised 2 : 2′-diaminodiphenyl sulphide and β-naphthol.

Treatment of the sulphuric acid solution of the tetrazonium salt with aqueous cuprous chloride gives, not 2 : 2′-dichlorodiphenyl disulphide, but an orange-brown *complex* of benzthiadiazole and cuprous chloride, the yield of benzthiadiazole obtained by ether-extraction after addition of sodium hydroxide being about 84%.

Since the tetrazonium salt is decomposed by the action of water, coupling was carried out by direct addition of the concentrated sulphuric acid solution to alkaline solutions (or suspensions) of β-naphthol. The resultant products varied considerably with the nature of the alkali used. Three distinct reactions may occur which, fortunately, can be realised separately by coupling in aqueous solutions of (i) sodium hydroxide, (ii) sodium carbonate, and (iii) sodium hydrogen carbonate, sodium acetate, or pyridine.

In the first case, benzthiadiazole (V), the *disulphide* (III) (which dissolves in organic solvents

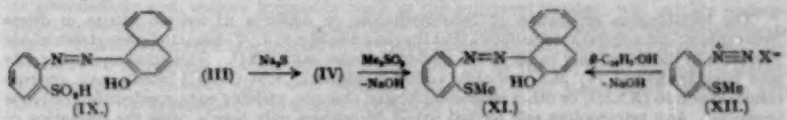
* *o*-Hydroxyazo-compounds are formulated in this paper for convenience as azo-compounds, although they may actually be phenylhydrazones (cf. Burawoy and Markowitsch, *Annalen*, 1933, **503**, 180).

with a characteristic violet colour), and bright red sodium o-(2-hydroxynaphthalene-1-azo)-benzenesulphinate (as IX) are formed.

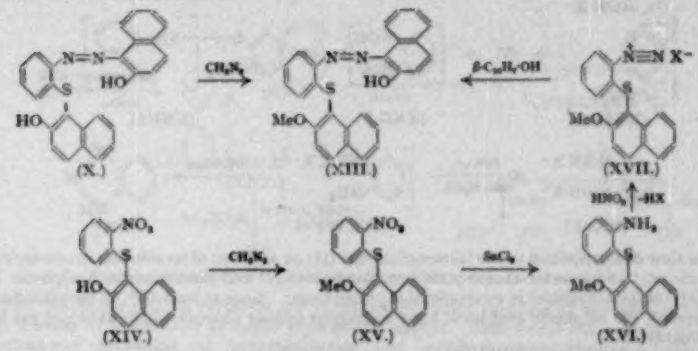
Coupling with the sodium salt of β-naphthol in excess of sodium carbonate yields benzthiadiazole and the reddish-brown *o-(2-hydroxynaphthalene-1-azo)phenyl 2-hydroxy-1-naphthyl sulphide* (X). No disulphide (III) or sulphinic acid (IX) can be isolated.

Finally, in excess of sodium hydrogen carbonate, sodium acetate, or pyridine, the disulphide (III) is obtained alone and in good yield.

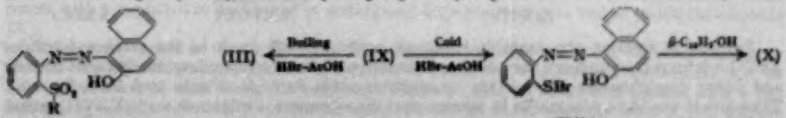
The structures of the various azo-compounds isolated were determined as follows. The disulphide (III) was reduced with sodium sulphide at room temperature and subsequently methylated with methyl sulphate to give 1-(o-*methylthiobenzeneazo*)-2-*naphthol* (XI), identical with a product synthesised unambiguously by coupling diazotised o-methylthioaniline (XII) with β-naphthol.



Acidification of an aqueous or alcoholic suspension of the sparingly soluble bluish-violet sodium salt of 1-(o-mercaptobenzeneazo)-2-naphthol with hydrochloric or acetic acid at room temperature yields the orange-red thiol itself, the first o-mercapto-azo-compound to be isolated. It is very sensitive to heat. In solution or in the solid state it is easily converted into a brown alkali-insoluble product. Its structure and the properties of o-mercapto-azo-compounds will be discussed elsewhere.



The sulphide (X) yields with diazomethane the *2'-methyl ether* (XIII), the hydroxyl group in 1-benzeneazo-2-naphthol being unreactive under these conditions (cf. Kuhn and Bär, *Annalen*, **1935**, **516**, 143). The structure of this ether was established by unambiguous synthesis from o-nitrophenyl 2-hydroxy-1-naphthyl sulphide (XIV) (Zincke and Farr, *ibid.*, 1912, **391**, 55) by methylation with diazomethane to (XV), reduction with stannous chloride to the *amine* (XVI), diazotisation to give (XVII), and finally coupling with β-naphthol.



(XVIII; R = Me)
(XIX; R = p-$NO_2C_6H_4CH_2$)

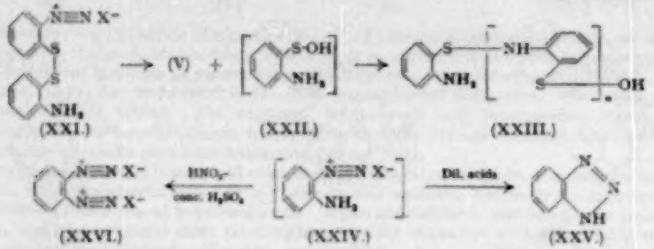
The sulphinic acid (IX) obtained from its water-soluble sodium salt by the addition of hydrochloric acid was characterised as o-*(2-hydroxynaphthalene-1-azo)phenyl methyl sulphone* (XVIII) and the corresponding p-*nitrobenzyl sulphone* (XIX). Its structure, besides being

suggested by general properties characteristic of sulphinic acids, was established by conversion (i) by hydrogen bromide in boiling glacial acetic acid into the disulphide (III), and (ii) by hydrogen bromide in cold glacial acetic acid into o-(*2-hydroxynaphthalene-1-azo*)*benzenesulphenyl bromide* (XX), and condensation of the latter with β-naphthol in quantitative yield to the sulphide (X).

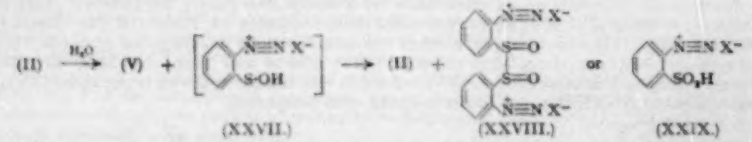
Aromatic sulphinic acids $ArSO_2H$ are known to yield, with hydrogen bromide in glacial acetic acid, either the corresponding sulphenyl bromides ArSBr or the disulphides ArS·SAr depending on the reaction temperature and the nature of the sulphinic acid (Fries and Schürmann, *Ber.*, 1914, **47**, 1195); and aromatic sulphenyl halides are known to react with β-naphthol in suitable conditions to form 1-arylthio-2-naphthols (Zincke and Farr, *loc. cit.*; Fries, *Ber.*, 1912, **45**, 2965).

Discussion.

The spontaneous separation of benzthiadiazole on addition of sodium nitrite in dilute hydrochloric and sulphuric acids shows that the diazotisation of **2 : 2'**-diaminodiphenyl disulphide proceeds, in the main, only as far as the monodiazonium salt (XXI). This spontaneously splits into benzthiadiazole (V) and probably aniline-2-sulphenic acid (XXII) which may undergo condensation to (XXIII) or other more complicated changes, yielding some unidentified resinous products. Any tetrazonium salt formed would decompose only slowly, with the formation of benzthiadiazole (cf. above). This is similar to the behaviour of o-phenylenediamine which cannot be tetrazotised in dilute acids, the monodiazonium salt (XXIV) spontaneously condensing internally with the formation of benztriazole (XXV) (Ladenburg, *Ber.*, 1870, **9**, 219), whereas in concentrated sulphuric acid the reaction proceeds to the stable tetrazonium salt (XXVI) (Hodgson and Walker, *J.*, 1935, 530).



The slow decomposition of the tetrazonium salt (II) on addition of its solution in concentrated sulphuric acid to ice-water should yield benzthiadiazole (V) and diazobenzene-2-sulphenic acid (XXVII) (or its anhydride) in equimolecular proportions. Since at least 70% of benzthiadiazole is recovered, the sulphenic acid must have undergone further changes which have not yet been fully elucidated.



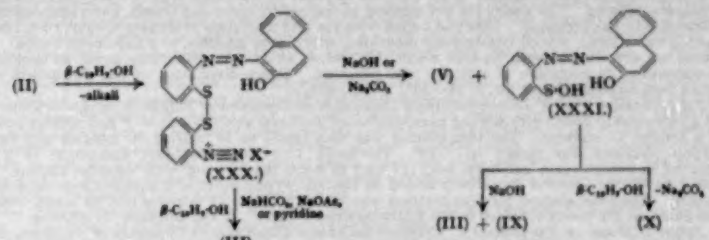
Substances forming the unstable sulphenic acids ArS·OH (such as the sulphenyl halides ArSX) are known to undergo easy disproportionation to the corresponding disulphides ArS·SAr and either disulphoxides ArSO·SOAr or sulphinic acids $ArSO_2H$ (Zincke and Farr, *loc. cit.*). Therefore it would be reasonable to assume that diazobenzene-o-sulphenic acid (XXVII) would behave similarly and would form the tetrazonium salt (II), which would again decompose yielding an additional amount of benzthiadiazole, and either the tetrazonium salt of **2 : 2'**-diaminodiphenyl disulphoxide (XXVIII) or diazobenzene-o-sulphinic acid (XXIX). However, coupling with alkaline β-naphthol yields, rather surprisingly, instead of the corresponding azo-compounds, the monosulphide (VIII). Our experiments do not afford any evidence for the

mechanism of the formation of tetrazotised 2 : 2'-diaminodiphenyl sulphide, but we have ascertained that it is not due to the presence of a small amount of 2 : 2'-diaminodiphenyl sulphide in the starting material.

The almost spontaneous formation of benzthiadiazole by the action of cuprous chloride on the tetrazonium salt (II) indicates either (i) its direct reduction, or (ii) its degradation to benzthiadiazole and diazobenzene-*o*-sulphenic acid (cf. above) followed by reduction of the latter. Since the degradation in absence of cuprous chloride is only slow, the former interpretation is more likely.

The reaction of the tetrazonium salt (II) with β-naphthol in sodium hydroxide solution is initiated by coupling with one mole of β-naphthol which is followed by degradation of the intermediate (XXX) to benzthiadiazole (V) and the salt of *o*-(2-hydroxynaphthalene-1-azo)-benzenesulphenic acid (XXXI). The latter, like all known substances forming sulphenic acids as intermediate with sodium hydroxide (such as the sulphenyl halides), will quickly undergo disproportionation to equimolecular quantities of the disulphide (III) and the sodium sulphinate (IX). This interpretation is supported (i) by the yields of disulphide and sulphinic acid obtained, which would correspond to about 90% of theory, and (ii) by the analogous disproportionation of the sulphenyl bromide (XX) with sodium hydroxide at room temperature, which is also initiated by the formation of the sodium sulphenate (XXXI).

For various reasons, it is unlikely that the degradation of the tetrazonium salt (II) to benzthiadiazole and sodium diazobenzene-*o*-sulphenate takes place first and is followed by the coupling of this diazo-compound with β-naphthol and, finally, disproportionation. Thus, the disulphide (III) is not formed if the tetrazonium solution in concentrated sulphuric acid is first added to sodium hydroxide, sodium carbonate, or sodium hydrogen carbonate alone and then quickly treated with β-naphthol. The separation of benzthiadiazole, *i.e.*, degradation, is spontaneous in these conditions.



Coupling of tetrazotised 2 : 2'-diaminodiphenyl disulphide with β-naphthol.

The disulphide (III) is certainly not produced by direct coupling of the tetrazonium salt with 2 moles of β-naphthol, as might superficially appear. This would not account (i) for the simultaneous formation of benzthiadiazole and *o*-(2-hydroxynaphthalene-1-azo)benzene-sulphinic acid, or (ii) for the results of the coupling in sodium carbonate solution. In these more weakly alkaline conditions, the rate of degradation of the tetrazonium salt (II) would, if different, be slower than in aqueous sodium hydroxide. The formation of the disulphide would, therefore, be expected to be more complete, whereas, at most, traces are formed.

The reaction in sodium carbonate solution will proceed first as in sodium hydroxide, but the sulphenic acid (XXXI), being comparatively stable under these more weakly alkaline conditions, reacts with β-naphthol in preference to undergoing disproportionation and so yields the sulphide (X).

There is no report in the literature of the behaviour of sulphenic acids, their anhydrides or halides towards cold sodium carbonate solution as compared with sodium hydroxide, but we have established (i) that when the sulphenyl bromide (XX) in benzene is shaken with a 2% sodium hydroxide solution disproportionation occurs at once, whereas with a 2% sodium carbonate solution this is comparatively slow, and (ii) that in presence of β-naphthol only a very small amount (< 5%) of the sulphide (X) is formed in the former case and an almost quantitative yield in the latter.

Coupling in aqueous pyridine, sodium hydrogen carbonate, or sodium acetate is also initiated by the formation of the intermediate (XXX). However, in these weakly alkaline or acid

conditions this product is sufficiently stable to allow coupling with a second mole of β-naphthol to take preference over degradation. Thus, only the disulphide (III) is formed. Although this is the most economical method for the preparation of this substance, the yields obtained (40—65%) and the isolation of small amounts of benzthiadiazole indicate that coupling is accompanied by a partial degradation of the tetrazonium salt.

Finally, it should be mentioned that the disulphide (III) is not stable to alkali, being converted, on prolonged contact at room temperature or on heating, into the sulphinic acid (IX). Undoubtedly this reaction is initiated by hydrolysis to the salts of 1-(*o*-mercaptobenzeneazo)-2-naphthol (IV) and the sulphenic acid (XXXI), which is a general reaction of disulphides (cf., *e.g.*, Schiller and Otto, *Ber.*, 1876, **9**, 1637; Fromm, *Annalen*, 1921, **426**, 313; Reissert and Manns, *Ber.*, 1928, **61**, 1308). Subsequently, (IV) is probably re-oxidised to the disulphide, and (XXXI) undergoes disproportionation to the disulphide and the sulphinic acid, which is, finally, the only product isolated.

The investigation is being continued in various directions.

Experimental.

Diazotisation of 2 : 2′-Diaminodiphenyl Disulphide in Dilute Mineral Acids.—The suspension of the amine hydrochloride obtained by intimate mixing of 2 : 2′-diaminodiphenyl disulphide (5 g.) and concentrated hydrochloric acid (20 c.c.) was poured into water (300 c.c.) at 0°. Sodium nitrite (4 g.) in a small amount of water was added. Benzthiadiazole and a brown resinous product, insoluble in water and ether, immediately separated. Extraction with ether yielded crude benzthiadiazole, m. p. 31—33° (m. p. when pure, 35°) (3·2 g., 58%). After filtration the aqueous layer was added to an alkaline solution of β-naphthol. 0·17 G. of an alkali-insoluble brown azo-compound separated. The experiment was repeated with sulphuric instead of hydrochloric acid and with increasing amounts of acid; the results were similar, yields of benzthiadiazole varying between 45 and 60%.

Diazotisation of 2 : 2′-Diaminodiphenyl Disulphide according to Guha and Ghosh (loc. cit.).—2 : 2′-Diaminodiphenyl disulphide (3 g.) and concentrated hydrochloric acid (7·5 c.c.) were mixed with mechanical stirring. The amine did not dissolve as claimed by Guha and Ghosh, but a suspension of the hydrochloride was obtained. This was cooled with ice, and a solution of sodium nitrite (1·8 g.) in water (15 c.c.) was added. An oil immediately separated, which soon solidified to a light-brown solid. When filtered off and washed with ice-cold water this melted at *ca.* 24°, solidifying again on cooling. No decomposition or evolution of nitrogen was observed. Steam-distillation of the precipitate yielded almost pure benzthiadiazole (m. p. 34—35°; 1·5 g., 46%).

Tetrazotisation of 2 : 2′-Diaminodiphenyl Disulphide in Concentrated Sulphuric Acid.—Sodium nitrite (3·6 g.) was slowly added with stirring to concentrated sulphuric acid (25 c.c.) at 0° and stirring continued for a further 10 minutes. The temperature was then raised to 70° during 20 minutes and the clear solution obtained was cooled to −10°. Powdered 2 : 2-diaminodiphenyl disulphide (5 g.) was dissolved in concentrated sulphuric acid (17 c.c.) at room temperature with vigorous stirring. After cooling to 0°, the solution was slowly added to the nitrosylsulphuric acid solution kept in a freezing mixture. The time allowed for diazotisation was varied between 10 minutes and 24 hours, with very little effect on the yields obtained in the following experiments. It was generally 30 minutes.

Action of Water on Tetrazotised 2 : 2′-Diaminodiphenyl Disulphide in Concentrated Sulphuric Acid.—The tetrazonium salt solution from the disulphide (5 g.) was poured into ice-water (800 c.c.). On extracting the solution immediately with ether, no benzthiadiazole was obtained. The solution with β-naphthol in aqueous sodium hydroxide gave the red precipitate of di-*o*-(2-hydroxynaphthalene-1-azo)-phenyl disulphide (III) recognised by its characteristic violet colour in benzene. After 30 minutes, crystalline benzthiadiazole began to separate and coupling as indicated above to decrease. After 4—6 hours, the solution ceased to yield any violet product with alkaline β-naphthol, indicating complete degradation of the tetrazonium salt. Extraction with ether yielded almost pure benzthiadiazole, m. p. 34—35° (4·0 g., 73%). The aqueous layer was poured into a solution of β-naphthol (3 g.) and sodium hydroxide (80 g.) in water (700 c.c.) at 0°. Alkali-insoluble, brown di-*o*-(2-hydroxynaphthalene-1-azo)phenyl sulphide (VIII) (0·5 g., 5%) was precipitated, which crystallised from xylene as reddish-orange needles, m. p. 284—286° (cf. below). The experiment was repeated, but the tetrazonium solution was kept at 0° up to 4 days before and after addition to water. The yields of benzthiadiazole and sulphide varied little.

Action of Aqueous Sodium Hydroxide, Sodium Carbonate, or Sodium Hydrogen Carbonate on Tetrazotised 2 : 2′-Diaminodiphenyl Disulphide.—A tetrazonium salt solution prepared from the disulphide (5 g.) was poured into ice-water (800 g.) containing sodium hydroxide (80 g.). Crude benzthiadiazole (2·7 g., 50%) separated immediately. The mother-liquor did not yield any azo-compound on subsequent quick addition of β-naphthol. Similar results were obtained when sodium hydroxide was replaced by sodium carbonate or sodium hydrogen carbonate.

Di-o-(2-hydroxynaphthalene-1-azo)phenyl Sulphide (VIII).—2 : 2′-Diaminodiphenyl sulphide (1·3 g.) was dissolved in concentrated hydrochloric acid (6 c.c.), glacial acetic acid (20 c.c.), and boiling water (100 c.c.). Sodium nitrite (0·85 g.) in a small amount of water was added at 0° and the mixture stirred for 10 minutes. The tetrazonium salt solution was poured into a solution of β-naphthol (3·5 g.) and sodium hydroxide (30 g.) in water (300 c.c.). The precipitated *sulphide* (2·8 g., 88%) was filtered off. It was obtained from xylene as reddish-orange needles, m. p. 284—286° (Found: N, 10·7; S, 5·9. $C_{32}H_{22}O_2N_4S$ requires N, 10·6; S, 6·1%).

Action of Cuprous Chloride on Tetrazotised 2 : 2′-Diaminodiphenyl Disulphide in Concentrated Sulphuric Acid.—A tetrazonium salt solution prepared from 5 g. of the disulphide was poured into an

ice-cold solution of cuprous chloride (10 g.) in concentrated hydrochloric acid (90 c.c.), whereupon the brown *complex* (8·0 g.) of benzthiadiazole and cuprous chloride immediately separated (Found: Cu, 27·2. $2C_6H_4N_2S,Cu_2Cl_2$ requires Cu, 27·0%).

This experiment was repeated, but, without isolation of the complex, sodium hydroxide was added and the benzthiadiazole extracted with ether. The yield of almost pure product (m. p. 34—35°) was 4·6 g. (85%).

Coupling of Tetrazotised 2 : 2′-Diaminodiphenyl Disulphide with β-Naphthol.—(i) *Coupling in sodium hydroxide solution.* A solution of tetrazotised disulphide (5 g.) in concentrated sulphuric acid was slowly added to a solution of β-naphthol (6 g.) and sodium hydroxide (80 g.) in water (500 c.c.) and kept below 5° by the addition of ice (1·5 kg.). *Di-(o-2-hydroxynaphthalene-1-azo)phenyl disulphide* (III), contaminated by some benzthiadiazole and sodium sulphate separated. After 2 hours, the precipitate (3·3 g., 89%) was filtered off, washed with warm water and digested with methyl alcohol (100 c.c.). Crystallisation from benzene gives dark red needles (with a green lustre), m. p. 233—234°, containing one mole of benzene which is slowly lost at room temperature and quickly at 100° (in a vacuum) (Found: N, 10·3; S, 11·4. $C_{32}H_{22}O_2N_4S_2$ requires N, 10·0; S, 11·5%). This disulphide dissolves in organic solvents with a violet, and in concentrated sulphuric acid with an orange, colour.

The filtrate was treated with carbon dioxide. A red precipitate of sodium o-(2-hydroxynaphthalene-1-azo)benzenesulphinate (IX) separated, contaminated by β-naphthol. After filtration, washing with a small amount of water, and drying, it was digested with chloroform (100 c.c.) and collected. Yield: 2·1 g. (91%). M. p. 290° (decomp.). Acidification of an aqueous solution of the salt with hydrochloric acid yielded the reddish-brown crystalline free *acid*, m. p. 165—166°, sparingly soluble in water and alcohol and dissolving in concentrated sulphuric acid with deep violet colour (Found: N, 9·3. $C_{16}H_{12}O_3N_2S$ requires 9·0%).

Steam-distillation of the mother-liquor from the main reaction yielded almost pure benzthiadiazole, m. p. 34—35° (1·9 g., 70%).

(ii) *Coupling in sodium carbonate solution.* A sulphuric acid solution of tetrazotised 2 : 2′-diaminodiphenyl disulphide (5 g.) was slowly added to a well-stirred solution of β-naphthol (20 g.) in 5% aqueous sodium hydroxide (120 c.c.) and sodium carbonate (100 g.) in water (800 c.c.). After 2 hours, the precipitate of *o-(2-hydroxynaphthalene-1-azo)phenyl 2-hydroxy-1-naphthyl sulphide* (X), contaminated with sodium sulphate, β-naphthol, and benzthiadiazole, was filtered off, washed with hot water and digested with methyl alcohol (100 c.c.). Yield: 5·6 g. (66%). Crystallisation from xylene gives brownish-red needles, m. p. 226—227° (Found: N, 6·8; S, 7·8. $C_{32}H_{22}O_2N_4S$ requires N, 6·6; S, 7·6%). This compound is sparingly soluble in cold organic solvents and in hot aqueous hydroxide with a brown colour. Concentrated sulphuric acid dissolves it with a violet colour which rapidly becomes brown.

Steam-distillation of the main mother-liquor yielded almost pure benzthiadiazole, m. p. 34—35° (1·3 g., 48%).

(iii) *Coupling in sodium hydrogen carbonate, sodium acetate, or pyridine.* A tetrazonium salt solution prepared from 2 : 2′-diaminodiphenyl disulphide (5 g.) was dropped into a well-stirred slution of urea (3 g.) and sodium hydrogen carbonate (160 g.) in water (2000 c.c.) to which β-naphthol (30 g.) in alcohol (200 c.c.) had been added. The temperature was kept below 5° by the addition of ice. The precipitate of the disulphide (III) and β-naphthol was filtered off and digested twice with 3% aqueous sodium hydroxide to remove β-naphthol. The yield of crude *disulphide* (III) was 6·8 g. (61%). On steam-distillation of the mother-liquor 0·25 g. of benzthiadiazole was recovered. No sulphide (X) or sulphinic acid (IX) could be isolated from the alkaline extracts.

Similar results were obtained when sodium hydrogen carbonate was replaced by sodium acetate or pyridine. The yields of disulphide varied between 40 and 65%.

1-(o-*Methylthiobenzeneazo*)-2-*naphthol* (XI).—(i) *Preparation from the disulphide* (III). A suspension of (III) (0·5 g.) in methyl alcohol (40 c.c.) was shaken for 2 hours at room temperature with a solution of sodium sulphide nonahydrate (1 g.) in water (10 c.c.). Some dark violet, sparingly soluble sodium salt of 1-(o-mercaptobenzeneazo)-2-naphthol (IV) separated. Water (100 c.c.) was added to the suspension, followed by 4 additions of 10% aqueous sodium hydroxide (10 c.c. each) and methyl sulphate (0·35 g. each), with vigorous shaking. 1-(o-*Methylthiobenzeneazo*)-2-*naphthol* (XI), which separated almost pure in quantitative yield, crystallised from ethyl alcohol in red needles, m. p. 163—164° (Found: N, 9·8. $C_{17}H_{14}ON_2S$ requires N, 9·6%).

(ii) *Preparation from* o-*methylthioaniline.* To the aniline derivative (2 g.) in 10% hydrochloric acid (15 c.c.), sodium nitrite (1·1 g.) in a small amount of water was added at 0°. The diazonium solution was poured into a solution of β-naphthol (2·2 g.) in excess of aqueous sodium hydroxide. The red azo-compound formed was filtered off (Found: N, 9·7%) (2·2 g., 52%) and crystallised from ethyl alcohol in red needles, m. p. 163—164° undepressed by admixture with the product obtained as in (i).

1-(o-*Mercaptobenzeneazo*)-2-*naphthol* (IV).—A solution of sodium sulphide nonahydrate (2 g.) in water (10 c.c.) was added to a suspension of the disulphide (III) (1 g.) in ethyl alcohol (55 c.c.), and the mixture shaken for 4 hours at room temperature. Water (150 c.c.) was then added, and the sodium salt of 1-(o-mercaptobenzeneazo)-2-naphthol (0·75 g.) which separated in dark violet needles with a metallic bronze lustre was filtered off. By salting out the filtrate with sodium chloride a further 0·2 g. of less pure compound was obtained (total yield 0·95 g., 88%) (Found: N, 9·2; S, 10·2; Na, 7·5. $C_{16}H_{11}ON_2SNa$ requires N, 9·3; S, 10·6; Na, 7·6%).

On acidifying a suspension of the sodium compound (0·5 g.) in ethyl alcohol (50 c.c.) and water (200 c.c.) with concentrated hydrochloric acid (20 c.c.), 1-(o-*mercaptobenzeneazo*)-2-*naphthol* (IV) was obtained. When heated to 100° or crystallised from warm solvents, it was converted into a brown, alkali-insoluble product. Purified by concentration of its benzene solution at room temperature in a vacuum, it was obtained in red plates, sintering at about 115° and melting at 183—185° (Found: N, 10·1; S, 11·2. $C_{16}H_{12}ON_2S$ requires N, 10·0; S, 11·4%).

o-(2-Hydroxynaphthalene-1-azo)phenyl 2-Methoxy-1-naphthyl Sulphide (XIII).—(i) *Methylation of the 2-hydroxy-1-naphthyl sulphide* (X). Diazomethane (1·2 g.) in ether (200 c.c.) was added to the phenolic sulphide (2 g.) in dry benzene (400 c.c.). After 24 hours, the solvents were removed and the

residue of *methoxy-sulphide* was recrystallised from benzene, forming red, monohydrated needles, sintering at about 125° and melting at 174—175° (Found: loss at 100°/15 mm., 4·2. $C_{17}H_{20}O_2N_2S,H_2O$ requires H_2O, 4·0%). After drying, the substance melts at 174—175° without sintering (Found: N, 6·5; S, 7·4; OMe, 6·9. $C_{17}H_{20}O_2N_2S$ requires N, 6·4; S, 7·3; OMe, 7·1%).

(ii) *o-Nitrophenyl 2-methoxy-1-naphthyl sulphide* (XV). A solution of *o*-nitrophenyl 2-hydroxy-1-naphthyl sulphide (Zincke and Farr, *loc. cit.*) (10 g.) in dry benzene (400 c.c.) was treated with diazomethane (3·6 g.) in ether (350 c.c.). After 24 hours the solvents were removed, and the residue, of almost pure *methoxy-sulphide* (XV) crystallised from benzene. It was obtained as yellow prisms, m. p. 174—175° (Found: N, 4·5; OMe, 9·5. $C_{17}H_{15}O_3NS$ requires N, 4·5; OMe, 9·9%).

(iii) *o-Aminophenyl 2-methoxy-1-naphthyl sulphide* (XVI). Stannous chloride dihydrate (12 g.) in concentrated hydrochloric acid (20 c.c.) was added at 100° to a solution of the above nitro-ether (5 g.) in glacial acetic acid (60 c.c.). After being heated on the steam-bath for 3 hours, the mixture was cooled. The precipitate of amino-sulphide stannichloride formed was filtered off, washed, and decomposed with 5% aqueous sodium hydroxide (200 c.c.). The free *amine* was collected and washed (2·6 g., 58%). Crystallisation from ethyl alcohol gave almost colourless plates, m. p. 136—137° (Found: N, 5·1; S, 11·2. $C_{17}H_{17}ONS$ requires N, 5·0; S, 11·4%).

(iv) *Coupling of diazotised o-aminophenyl 2-methoxy-1-naphthyl sulphide with β-naphthol.* The amine (0·5 g.) was dissolved in glacial acetic acid (12 c.c.) and concentrated hydrochloric acid (2 c.c.). After dilution with water (200 c.c.), sodium nitrite (0·15 g.) in a small amount of water was added at 0°. The diazonium solution was poured into a solution of β-naphthol (0·7 g.) and sodium hydroxide (12 g.) in water (100 c.c.). The red precipitate of o-(2-hydroxynaphthalene-1-azo)phenyl 2-methoxy-1-naphthyl sulphide (XIII) formed was filtered off, washed, and dried (0·78 g., 96%). It crystallised from benzene in red, hydrated needles, which sinter at about 125° and melt at 174—175° (Found: loss at 100°/15 mm., 4·5%). After drying they melt at 174—175° without sintering (Found: N, 6·5; S, 7·0; OMe, 6·9%). A mixed melting point with the dried product obtained as above showed no depression.

o-(2-Hydroxynaphthalene-1-azo)phenyl Methyl Sulphone (XVIII).—Sodium *o*-(2-hydroxynaphthalene-1-azo)phenylsulphinate (1 g.) was refluxed with methyl iodide (10 c.c.) for 6 hours. After cooling, the precipitate of *methyl sulphone* was filtered off, and washed repeatedly with 2% sodium hydroxide and finally with water. Crystallised from ethyl alcohol it formed brown needles, m. p. 184—185° (Found: N, 8·6. $C_{17}H_{14}O_3N_2S$ requires N, 8·6%).

p-Nitrobenzyl o-(2-Hydroxynaphthalene-1-azo)phenyl Sulphone (XIX).—The above-mentioned sodium sulphinate (2 g.) and *p*-nitrobenzyl bromide (2 g.) were refluxed in boiling ethyl alcohol (100 c.c.) for 30 hours. On dilution with water, a quantitative yield (2·7 g.) of *p-nitrobenzyl sulphone* was obtained. It crystallised from toluene in orange-red needles, m. p. 262—263° (Found: N, 9·6. $C_{23}H_{17}O_5N_3S$ requires N, 9·4%).

Conversion of the Sulphinic Acid (IX) *into the Disulphide* (III).—48% Hydrobromic acid (3 c.c.) was slowly added to a boiling suspension of the sulphinic acid (IX) (1 g.) in glacial acetic acid (25 c.c.). The solid went into solution. The cooled mixture was treated with water (400 c.c.). The disulphide (III) separated in quantitative yield (0·9 g.). Crystallisation from benzene gave a product, m. p. 233—234°, alone or mixed with the product obtained by coupling tetrazotised 2 : 2′-diaminodiphenyl disulphide with β-naphthol.

Conversion of the Sulphinic Acid into o-(2-Hydroxynaphthalene-1-azo)phenyl 2-Hydroxy-1-naphthyl Sulphide (X).—(i) *o-(2-Hydroxynaphthalene-1-azo)phenylsulphenyl bromide* (XX). The sulphinic acid (IX) (2 g.), suspended in glacial acetic acid (50 c.c.) containing 48% hydrobromic acid (5 c.c.) and shaken for 48 hours at room temperature, slowly went into solution, and the *sulphenyl bromide* (XX) separated quantitatively as a fine dark-red crystalline powder. This was filtered off, washed with glacial acetic acid and finally with light petroleum. It melted at 184—186° (Found: N, 7·8; Br, 22·0. $C_{16}H_{11}ON_2BrS$ requires N, 7·8; Br, 22·3%).

(ii) *Condensation of the sulphenyl bromide with β-naphthol.* A mixture of the above sulphenyl bromide (0·5 g.) and β-naphthol (0·5 g.) was heated at 110—115°, hydrogen bromide being evolved and the liquid mass becoming gradually more viscous. After 15 minutes the reaction mixture was cooled and digested with methyl alcohol in order to remove the excess of β-naphthol. The insoluble residue consisted of almost pure *o*-(2-hydroxynaphthalene-1-azo)phenyl 2-hydroxy-1-naphthyl sulphide (0·55 g., 93%). Crystallisation from xylene yielded brownish-red needles, m. p. 226—227° alone or mixed with the product obtained by coupling tetrazotised 2 : 2′-diaminodiphenyl disulphide with β-naphthol in sodium carbonate solution.

Reaction of o-(2-Hydroxynaphthalene-1-azo)benzenesulphenyl Bromide with β-Naphthol and Sodium Carbonate or Sodium Hydroxide Solution.—(i) The sulphenyl bromide (0·5 g.) and β-naphthol (1·0 g.) in benzene (30 c.c.) were shaken with 2% aqueous sodium carbonate (40 c.c.) for 48 hours at room temperature. The aqueous layer contained only traces of coloured products. The benzene layer was washed with 2% aqueous sodium hydroxide and evaporated to dryness. The residue consisted of slightly impure sulphide (X) (0·46 g., 78%), which yielded a pure product m. p. 226—227°, after one crystallisation from xylene.

(ii) The experiment was repeated, but the sodium carbonate solution was replaced by 2% aqueous sodium hydroxide (30 c.c.). The benzene layer developed spontaneously the violet colour of the disulphide (III) which disappeared during the continued shaking. After 48 hours it contained only a small quantity (0·03 g.) of the crude sulphide (X). The aqueous layer was saturated with sodium chloride, whereupon sodium o-(2-hydroxynaphthalene-1-azo)benzene-2-sulphinate, m. p. 290° (decomp.), separated in almost quantitative yield.

Action of Sodium Hydroxide on the Disulphide (III).—The disulphide (0·5 g.) was refluxed for 3 hours with sodium hydroxide (2 g.) in aqueous ethyl alcohol (1 : 1; 40 c.c.). The solution obtained was diluted with water (50 c.c.) and extracted with benzene, from which a small amount of unchanged starting material (0·07 g.) was recovered. The aqueous layer was acidified with concentrated hydrochloric acid, and the precipitate of the sulphinic acid (IX), m. p. 164—166°, (0·44 g., 80%), collected.

Action of Sodium Hydroxide on o-(2-Hydroxynaphthalene-1-azo)benzenesulphenyl Bromide.—The

sulphenyl bromide (0·5 g.), benzene (100 c.c.), and 2% aqueous sodium hydroxide (50 c.c.) were shaken at room temperature for 1 hour. The benzene layer was washed with dilute sodium hydroxide solution in order to remove small amounts of the sulphinic acid (IX) and finally evaporated to dryness. The residue consisted of almost pure di-*o*-(2-hydroxynaphthalene-1-azo)phenyl disulphide, m. p. 230—233° (0·25 g., 96%). The alkaline aqueous layer was treated with concentrated hydrochloric acid, and the precipitated sulphinic acid (m. p. 164—165°; 0·10 g., 69%), collected.

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94A. *Colouring Matters of the Aphididæ. Part II. Colouring Matters from* Aphis fabæ.

By J. P. E. HUMAN, A. W. JOHNSON, S. F. MACDONALD, and A. R. TODD.

An investigation leading to the isolation of four related colouring matters of a new type from the common bean aphid (*Aphis fabæ*) is described. The hæmolymph of the living insects contains the yellow *protoaphin-fb*, which is converted enzymically after the death of the insects into the fluorescent yellow *xanthoaphin-fb*. Protoaphin-*fb* can be isolated only from freshly collected insects which have been killed by a method (*e.g.*, quick heating) which simultaneously inactivates enzymes. Xanthoaphin-*fb* is unstable and undergoes ready conversion, particularly in presence of acids, first into the fluorescent, orange *chrysoaphin*-fb, and then into the fluorescent, carmine-red *erythroaphin*-fb. Preliminary chemical investigation of erythroaphin-*fb* indicates that it is a polycyclic quinone containing 2 phenolic hydroxyl groups; on oxidation with nitric acid it yields mellitic acid.

Very similar pigments are obtained from other species of Aphididæ, and the nomenclature adopted includes the use of suffix letters indicative of the species of origin.

IN a preliminary communication (Duewell, Human, Johnson, MacDonald, and Todd, *Nature*, 1948, **162**, 759), which we regard as Part I of the present series of papers, we gave a general account of our initial investigations on a remarkable group of fluorescent colouring matters which occur in the hæmolymph of many species of Aphididæ, or which derive from precursors present in the hæmolymph. These pigments we propose to describe in general as *aphins*. In each species there are four aphins to be considered (*a*) the *protoaphin* present in the living insect, (*b*) the *xanthoaphin* into which protoaphin is converted by enzymic action on the death of the insect, (*c*) *chrysoaphin* produced when xanthoaphin is kept in solution, and (*d*) *erythroaphin* which is formed by a similar transformation of chrysoaphin and which represents the moderately stable end-product of the series. The conversions (*b*) ⟶ (*c*) ⟶ (*d*) occur spontaneously in crude extracts of the insects and appear to be independent of the presence of air, although they are enormously accelerated by heat or by acids or alkalis; the characteristic visible absorption spectra of the pigments make it easy to follow the conversions and to detect the individual pigments in solution by means of a hand-spectroscope. The existence of this series of pigments and their remarkable transformations were recorded in some detail by Sorby nearly eighty years ago (*Quart. J. Microscop. Sci.*, 1871, ii (N.S.), 352), but until now his work seems to have escaped the notice of other investigators. Thus Blount (*J.*, 1936, 1034) has reported the isolation of two aphid colouring matters lanigerin and strobinin (respectively a chrysoaphin and an erythroaphin on our nomenclature), and Schulz (*Biochem. Z.*, 1922, **127**, 122) has recorded some observations on the pigments of the woolly aphid (*Eriosoma lanigerum*) without apparently being aware of Sorby's pioneer work. Other colouring matters apparently unrelated to the aphins have also been detected by us in certain Aphididæ and will be described later; whether they are related to the pigments of *A. gossypii*, examined by Wall (*Ann. Entomol. Soc. Amer.*, 1933, **26**, 425), is at present unknown.

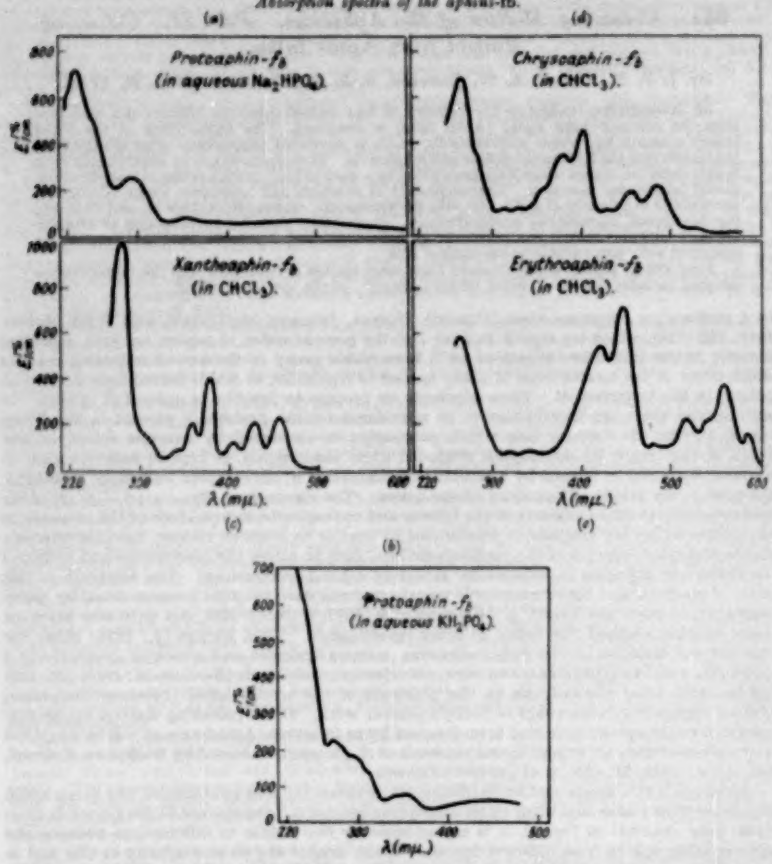
Although it is a simple matter to distinguish between the four aphins from any given aphid species by their visible and ultra-violet absorption spectra (cf. the spectra of the pigments from *Aphis fabæ* recorded in Fig. 1), it is not possible by this means to differentiate between the corresponding aphins from different species. Since, despite the close similarity in this and in many other respects, certain differences can nevertheless be detected in *X*-ray diffraction patterns and in infra-red absorption spectra, we have proposed that a two-letter suffix, indicative of the species of origin, be added to the name of each pigment until the question of identity or otherwise of corresponding pigments in the various species can be finally settled (Duewell, Human, Johnson, MacDonald, and Todd, *loc. cit.*). The present paper therefore deals with the isolation and preliminary examination of *protoaphin*-fb, *xanthoaphin*-fb, *chrysoaphin*-fb, and *erythroaphin*-fb, the pigments obtained from *Aphis fabæ*. This aphid is very prevalent in Britain and is the "black fly" which attacks cultivated broad beans (*Vicia faba*) during early

summer with depressing regularity; it also occurs on a variety of other hosts, *e.g.*, members of the beetroot family. In our experiments the insect was obtained mainly from heavily infested, cultivated broad bean plants in Cambridgeshire.

Although the actual pigment content of *A. fabæ* is *ca.* 0·8% of the weight of live insects, the development of suitable methods for isolating the various aphins in a pure condition has been a slow and tedious matter. This was caused in part by our failure to appreciate at the outset of

FIG. 1.

Absorption spectra of the aphins-fb.



our researches that we were dealing with a group of very labile substances capable of undergoing the series of interconversions mentioned above, and in part to the necessity of devising methods whereby insects could be collected as far as possible alive and undamaged. An added complication was the difficulty of obtaining the large amounts of insects necessary and the development of methods whereby, since they are seasonal in habit, the collected insects could be stored for later study without gross decomposition of the aphins. It is not proposed to discuss in detail the various methods we have from time to time employed during the progress of the work;

instead descriptions of methods will be confined essentially to those which we finally adopted for the isolation of the main bulk of *A. fabæ* pigments used in the present studies.

When undamaged specimens of *A. fabæ* are killed by quick heating to 70°, enzymes are simultaneously inactivated, and, if the insects are then crushed with aqueous acetone or aqueous methanol, extracts are obtained which show no characteristic bands in their visible-light absorption spectra and yield no fluorescent material on extraction with light petroleum. The colour of such crude extracts varies from red to greenish-brown in different batches of insects collected at different times. This is caused by the presence in the insects of varying amounts of a green material, apparently unrelated to the aphins. This green substance, which is probably a mixture of pigments, has not been closely examined, but its presence does not interfere with the isolation of the aphins; it is soluble in water, is unaffected by fermentation of the insect material, and is not extractable with light petroleum. When the filtered crude extracts are acidified and the acetone or methanol removed, protoaphin-*fb* separates as yellow needles. Protoaphin-*fb* contains only carbon, hydrogen, and oxygen, is yellow in acid aqueous solution and purplish-red at pH values >5·5. If, however, living specimens of *A. fabæ* are crushed with cold water and the suspension set aside at room temperature for an hour, the red colour of the protoaphin disappears and extraction of the resulting suspension with aqueous acetone gives bright yellow extracts with a strong bluish-green fluorescence. These extracts apparently contain no protoaphin-*fb*, since the yellow pigment they contain can be completely extracted from them with light petroleum; spectroscopic examination shows indeed that they contain mainly the water-insoluble xanthoaphin-*fb*. This conversion of protoaphin-*fb* into xanthoaphin-*fb* in crude extracts is best carried out by using, in place of water, buffer solution of pH 6·5. If the enzymic action occurs under unfavourable conditions, *e.g.*, on preserving dead but intact insects at temperatures $> -10°$ for some weeks, the protoaphin-*fb* is degraded to various ill-defined products which can neither be extracted with light petroleum nor transformed into other aphins. Although the enzyme responsible for the conversion has not yet been isolated, there can be no doubt that protoaphin-*fb* is the precursor of xanthoaphin-*fb*. The crystalline protoaphin is converted into the xanthoaphin by treating solutions buffered to pH 6—7 with freshly crushed insects; under these conditions one crushed insect contains sufficient enzyme to convert some thirty times its own content of protoaphin. Again, although xanthoaphin-*fb*, chrysoaphin-*fb*, and erythroaphin-*fb* are all obtainable from dead fermented insects, they are not present to any appreciable extent in living insects. This follows from the facts that only protoaphin-*fb* is found in extracts of insects killed by being heated to 70° and that when living insects are crushed in concentrated sulphuric acid the solutions obtained do not show the strong absorption bands characteristic of the fluorescent aphins.

For the preparation of xanthoaphin, chrysoaphin, and erythroaphin, fermented insects are extracted with 80% acetone. Most of the fat in the extracts is separated by cooling and the solution is then shaken with light petroleum. Evaporation of the petroleum layer gives, as a rule, a granular precipitate of the mixed aphins in varying proportion contaminated by some fat or wax which can be removed by re-extraction with light petroleum. Owing to the seasonal occurrence of *A. fabæ*, and indeed of all the Aphididæ, and the strictly limited period during which they can be collected in quantity, it was necessary to find some way of preserving the insects so that they could later be extracted. It has been found that this end can be achieved by storage at temperatures below $-10°$ and that insects so stored for periods up to at least six months form suitable starting material for the preparation of chrysoaphin-*fb* and erythroaphin-*fb*, using a slight variation of the above method of extraction. For the xanthoaphin, fresh insects are preferable, and we have not been able to prepare protoaphin-*fb* in a pure state from preserved insects.

Separation and purification of the mixed aphins obtained by the above extraction procedures depend on the conversions xanthoaphin-*fb* ⟶ chrysoaphin-*fb* ⟶ erythroaphin-*fb* and on the fact that, although in most solvents the solubilities of the aphins decrease in the order named, this is reversed in carbon tetrachloride in which xanthoaphin-*fb* is the least soluble. The preparation of pure xanthoaphin-*fb* by direct crystallisation of the mixed aphins is satisfactory only when it is present in a relatively high proportion. It holds small amounts of solvents tenaciously and it is preferable to recrystallise it from ether immediately before analysis. Xanthoaphin-*fb* is unstable in solution or in the solid state in presence of light and changes into the orange chrysoaphin-*fb*; the change is greatly accelerated by heat or by acids, and it is advisable to carry out chemical manipulations with the substance rapidly and as far as possible in the absence of light.

Chrysoaphin-*fb* can be obtained by concentrating the carbon tetrachloride mother-liquor

obtained after xanthoaphin has been separated from the crude mixed aphins. It may also be prepared from the yellow crystalline xanthoaphin by mild acid treatment, *e.g.*, by warming it with commercial chloroform; mixtures of xanthoaphin and chrysoaphin may be worked up for the latter by similar treatment. Like xanthoaphin-*fb*, chrysoaphin-*fb* has no definite melting point and on heating appears to undergo partial conversion into erythroaphin-*fb* before decomposing.

Erythroaphin-*fb*, which forms beautiful carmine-red needles, can be isolated from the final crystallisation mother-liquors of the mixed aphins. It can also be conveniently prepared from xanthoaphin-*fb* or chrysoaphin-*fb*, or from mixtures of these pigments, by warming their solutions in ethyl acetate with a little formic acid or by treating them in ethanolic solution with mineral acid. Purification of crude erythroaphin-*fb* is normally effected by recrystallisation from ethanol–chloroform; chromatography has not been found very useful, as the pigment is too strongly adsorbed on most of the common adsorbents.

Erythroaphin-*fb*, being the end-product and the most stable member of the aphin-*fb* series, was the most readily available material in the earlier stages of our work and has therefore been the subject of most investigation so far. Like the other aphins, it has no melting point and on heating it gradually chars and decomposes above 250°; it cannot be sublimed even in a high vacuum. It is moderately soluble in chloroform, carbon tetrachloride, benzene, or acetone, and only sparingly so in most of the other common organic solvents. In dry pyridine it dissolves readily but solutions in this solvent undergo some chemical change on storage. Solutions in organic solvents or in concentrated sulphuric acid are red and show a red fluorescence, which is particularly intense in ultra-violet light. Solutions in aqueous pyridine, sodium hydroxide, and ammonia are bright green and deposit green precipitates on storage, and similar solutions are obtained under certain conditions with sodium carbonate or hydrogen carbonate. On treatment with acetic anhydride containing a drop of sulphuric acid, the solution, at first red, changes rapidly through green to pure blue with an intense red fluorescence. This striking colour reaction was first described by Blount (*loc. cit.*) for strobinin (erythroaphin-*st*) and is characteristic of all the erythroaphins we have examined. Since under the acid conditions used, xanthoaphins and chrysoaphins are converted into the corresponding erythroaphins, it may be regarded as a general reaction for all the fluorescent aphins.

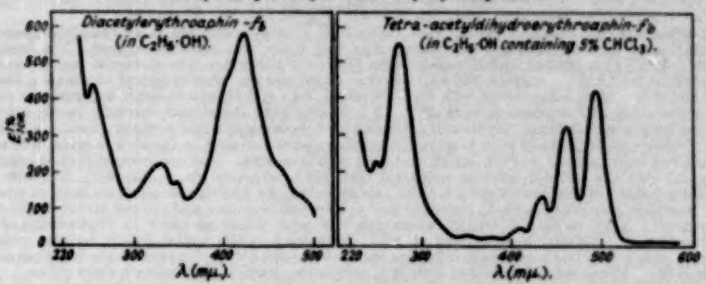
Erythroaphin-*fb* contains neither nitrogen, sulphur, nor halogens; it contains no methoxy-groups (Zeisel), and chromic acid oxidation (Kuhn–Roth) suggests the presence of several *C*-methyl residues. Difficulties have been encountered in obtaining consistent analytical values, but the results of a series of analyses indicate that it has a formula $C_{34}H_{32-34}O_8$. Attempts to determine the molecular weight of erythroaphin-*fb* by cryoscopic and ebullioscopic methods gave values ranging from 400 to 700, and similar inconsistent results were obtained using the Signer vapour-pressure method. Acyl derivatives of erythroaphin, although they seemed more suitable for these determinations on account of their greater solubility, also gave variable results. *X*-Ray crystallographic examination, however, indicates that erythroaphin-*fb* has a molecular weight of 660, 519, or 1038 $\pm$ 3% according to whether the unit cell contains 8, 4, or 2 molecules. Of these values only 519 $\pm$ 3% seems to be in accord with the behaviour of erythroaphin-*fb* on reduction and reductive acetylation and with the admittedly variable results of molecular-weight determinations by other methods. Acetylation yields *diacetyl-erythroaphin*-fb ($C_{34}H_{28-32}O_{10}$) which is insoluble in cold alkali and is readily hydrolysed to erythroaphin-*fb*. A *dibenzoyl* derivative has also been prepared, but attempted methylation failed to yield crystalline products. Hydrogenation of erythroaphin-*fb* in presence of a platinum catalyst or reduction with sodium dithionite gives a pale brown, fluorescent solution of a dihydroerythroaphin, which is rapidly re-oxidised in air to the original erythroaphin (identified by *X*-ray powder photography). These findings strongly suggest the presence of a quinonoid structure, and also the absence of non-reversibly reducing groups such as ethylenic linkages, aldehydo-groups etc. The presence of a quinonoid structure is confirmed by the behaviour of erythroaphin-*fb* or its diacetyl derivative on reductive acetylation, when the orange *tetra-acetyl-dihydroerythroaphin*-fb ($C_{34}H_{30-32}O_{12}$) is obtained. This derivative is insoluble in alkali and resists catalytic hydrogenation. Its formation eliminates a C_{16} formula for erythoaphin-*fb*, since reductive acetylation must introduce at least two acetyl groups. Evidence pointing to a C_{32} formula has also been obtained by quantitative microhydrogenation of erythroaphin-*fb* and its diacetyl derivative. A C_{40} formula (*i.e.*, *M*, 1038 $\pm$ 3%) would require the presence of two quinone groups and the absence of an intermediate absorption spectrum or of any break in the hydrogenation at the half-way stage is regarded as evidence against such a hypothesis. The absorption curves of diacetylerythroaphin-*fb* and tetra-acetyldihydroerythroaphin-*fb* are reproduced in Fig. 2.

In the erythroaphin-*fb* molecule, two oxygen atoms thus seem to be present in hydroxy-groups and two in a quinone system. The function of the remaining oxygens is still unknown, as is the nature of the nucleus. That the pigment is polynuclear would seem probable from the fact that oxidation with concentrated nitric acid yields mellitic acid, identified as its hexamethyl ester. In certain of its reactions erythroaphin-*fb* shows a resemblance to the photodynamic pigment of St. John's wort, hypericin, $C_{30}H_{16}O_8$ (Brockmann *et al.*, *Naturwiss.*, 1939, **27**, 550; *Annalen*, 1942, **553**, 1; Pace and McKinney, *J. Amer. Chem. Soc.*, 1941, **63**, 2570), and to the mould pigment oxypenicilliopsin (Oxford and Raistrick, *Biochem. J.*, 1940, **34**, 790). It is also of interest that Dhéré (*Compt. rend. Soc. Biol.*, 1939, **131**, 672; *Boissiera*, 1943, **7**, 423) has already remarked on the similarity between the ultra-violet fluorescence spectra of the lanigerin (chrysoaphin-*ln*) and strobinin (erythroaphin-*st*) of Blount (*loc. cit.*) and those of hypericin and oxypenicilliopsin. At present, however, there is insufficient chemical evidence to warrant any speculation on the nature of the relationship, if any, which may exist between erythroaphin-*fb* and these plant pigments.

So far little work has been done on the protoaphin, xanthoaphin and chrysoaphin from *A. fabæ*. The ready conversion of the last two into erythroaphin-*fb* complicates chemical study; thus, for example, when chrysoaphin-*fb* is acetylated the product is diacetyl-erythroaphin-*fb*. Elementary analysis gives values which correspond approximately to formulæ $C_{28}H_{36}O_{11}$ for xanthoaphin-*fb* and $C_{30}H_{44}O_9$ for chrysoaphin-*fb*. These formulæ,

FIG. 2.

Absorption spectra of derivatives of erythroaphin-fb.



although only provisional, are at any rate in agreement with our failure to detect any by-products in the conversion of them into erythroaphin-*fb* and suggest that the conversion involves dehydration with an increase in aromatic character.

Protoaphin-*fb* differs from the three fluorescent aphins derived from it both in its chemical properties and in its composition. Analytical results suggest for it a formula $C_{32}H_{48}O_{13}$. It is reversibly reduced by dithionite to a colourless, fluorescent material, and it is readily oxidised to colourless products by a variety of reagents. Whether the enzymic conversion of protoaphin-*fb* to xanthoaphin-*fb* is accompanied by loss of a carbohydrate residue (as a comparison of the provisional formulæ of the compounds might suggest) has not yet been determined, and a decision on this and other relevant points must await the results of further work now in progress. It must be emphasised that the formulæ given in this paper for protoaphin-*fb*, xanthoaphin-*fb* and chrysoaphin-*fb* are advanced merely to indicate that a simple relationship between them and erythroaphin-*fb* would not conflict with the analytical data, and they may require considerable revision when further evidence becomes available.

EXPERIMENTAL.

Collection of Material.—After trial of a variety of methods, that which involved collection of the infested portions of bean plants and removal of the insects by a washing procedure (see below) was adopted for general use. Although it is possible to store *A. fabæ* at temperatures $< -10°$ while still on the plants, it was found more satisfactory to remove them as soon as possible after the plants were collected and, after separating them from foreign insects, to keep the aphids in cold storage in glass bottles.

Protoaphin-fb.—Plant material bearing living insects was placed in a cylindrical basket of wire gauze (½" mesh) which fitted inside a beaker (10-l. capacity) containing sufficient water (usually 6 l.) at 70° to immerse the plants completely. After 3 minutes the beaker and contents were placed in a sink lined

with cotton gauze (cheese-cloth), and a strong jet of tap water was directed on one side of the basket. This had the effect of rotating the basket and washing the insects through the wire gauze, whereupon they passed out of the beaker with the stream of water and were collected on the cheese-cloth. After this operation, the beaker was removed and excess of water gently squeezed out of the insects before they were transferred to a beaker containing methanol (250 c.c. for each 100 g. of wet aphids).

The mixture of wet insects (100 g.) and methanol (150 c.c.) was ground in a Waring Blendor for 2 minutes. Hyflo Supercel (5 g.) was stirred into the suspension which was filtered through a thin layer of Supercel. The filter residue was again extracted with aqueous methanol (200 c.c. of 60%) in the Waring Blendor and filtered as before, and the combined extracts were diluted with an equal volume of methanol and extracted with light petroleum (b. p. 40—60°; 2 × 250 c.c.) to remove any traces of fluorescent aphins. The aqueous-methanolic layer was then concentrated under reduced pressure to 150 c.c., treated with active charcoal (6 g.; Darco G. 60) with stirring, and filtered. The filtrate at this point had pH *ca.* 5 and no longer became red at pH >7. The charcoal containing the adsorbed protoaphin-*fb* was thoroughly washed with water and eluted by being stirred with aqueous acetone (75%; 6 × 25 c.c.). On removal of the acetone from the eluate under reduced pressure, *protoaphin*-fb (0·25—0·5 g.) separated as small, flat, golden needles which were washed with water and dried. For further purification the product was dissolved in aqueous sodium hydroxide (*N*./100) and filtered, and the filtrate acidified to pH 4 with hydrochloric acid (*N*./100). The purified pigment had no m. p. and on heating gradually darkened and decomposed above 210° (Found, in material dried at 56°/0·1 mm.: C, 55·2; 55·8, 55·9; H, 5·8, 5·6, 5·6; active H, 1·41; C-CH_3 (Kuhn–Roth), 7·9. $C_{44}H_{44}O_{19}$ requires C, 55·4; H, 5·7%). Protoaphin-*fb* contains neither nitrogen, sulphur, halogens, phosphorus, nor methoxyl. It is readily soluble in dilute sodium hydroxide solution, 70—80% acetone, or pyridine, moderately so in 80% ethanol, 80% acetic acid, or aqueous dioxan, and very sparingly soluble in water, ether, light petroleum, chloroform, ethanol, acetone, or acetic acid. Solutions in water and organic solvents, including anhydrous pyridine, are yellow and those in sodium hydroxide and aqueous pyridine purplish-red. In concentrated sulphuric acid the pigment dissolved with decomposition, the solution darkening rapidly. Light absorption: (i) In KH_2PO_4 solution: Maxima at 2730, 3330, and 4420—4450 A.; $E^{1\%}_{1cm}$ = 220, 73, and 62 with inflections at 2920—2960, 3000—3060, and 3450—3470 A.; $E^{1\%}_{1cm}$ = 175, 140, and 70 respectively. (ii) In Na_2HPO_4 solution: Maxima at 2340, 2960, 3560, and 5180 A.; $E^{1\%}_{1cm}$ = 725, 250, 75, and 70.

Xanthoaphin-fb.—The live insects were washed off infected bean plants as described under the preparation of protoaphin-*fb* (above), except that cold water was used throughout. The fresh wet aphids (150 g.) were crushed with Sörensen buffer (150 c.c.; pH 6·2) in a large mortar and left at room temperature for 1 hour. Acetone (600 c.c.) was then added and the mixture ground in a Waring Blendor for 2 minutes. After being stirred with Hyflo Supercel (5 g.) and filtered through Supercel, the residue was re-extracted with aqueous acetone (80%; 3 × 25 c.c.) until the extract was only faintly coloured. The combined greenish-brown filtrate and extracts were concentrated under reduced pressure, a " boiling stick " being used to promote even evaporation, until separation of solid on the surface set in, whereupon the mixture was cooled to −10° by addition of solid carbon dioxide. The precipitated fat was separated (Supercel) and the clarified solution extracted with light petroleum (b. p. 40—60°; 3 × 500 c.c.), emulsions formed during the extraction being readily broken by addition of small amounts of acetone. The combined petroleum extracts normally had a light-yellow colour and showed strong bluish-green fluorescence; they contained mainly xanthoaphin-*fb* with small amounts of chrysoaphin-*fb* and erythroaphin-*fb*. Solvent was removed at >35° (bath-temp. >50°) under slightly reduced pressure, giving a pale brown residue of crude colouring matter (0·6—0·9 g.) which was normally free from all but traces of fat. The powder was washed with light petroleum, dried, and boiled with ether (80 c.c.). The ethereal extract was concentrated to smaller bulk (30 c.c.), acid-free carbon tetrachloride (30 c.c.) added, and the solution concentrated until crystallisation set in, whereafter it was cooled to 0°. The *xanthoaphin*-fb was collected and recrystallised from ether; it formed bright yellow needles (0·4 — 0·5 g.) which on heating did not melt but gradually decomposed above 210° (Found, in material dried at room temperature/0·1 mm. for 12 hours: C, 63·7, 63·5, 64·4, 64·3; H, 5·9, 5·5, 5·7, 5·9. $C_{30}H_{30}O_{11}$ requires C, 63·6; H, 5·3%). Qualitative tests for nitrogen, phosphorus, sulphur, and halogens were negative.

Xanthoaphin-*fb* is readily soluble in acetone, ethanol, pyridine, or ethyl acetate, moderately so in chloroform, ether, or benzene, and very sparingly in carbon tetrachloride or light petroleum; it is insoluble in water. Solutions in organic solvents or aqueous organic solvents at neutral or acid pH are bright yellow and show a bluish-green fluorescence even in daylight; in ultra-violet light the fluorescence is intense even for the solid substance. It dissolved readily in aqueous sodium hydroxide, giving a pink solution with a powerful yellowish-green fluorescence in ultra-violet light. Light absorption in chloroform: Maxima at 2820, 3580, 3780, 4050, 4290, and 4590 A.; $E^{1\%}_{1cm}$ = 992, 198, 400, 116, 205, and 228 respectively.

It is difficult to work with xanthoaphin-*fb* or at times even to purify it because of its great lability, particularly to traces of acid or to heat, under the influence of which it undergoes irreversible conversion into chrysoaphin-*fb* (see below). This conversion has frequently occurred during recrystallisation, presumably owing to the presence of unsuspected traces of acid. In the same way, crystalline xanthoaphin-*fb* is liable to undergo slow conversion on being kept for long periods in specimen tubes. Under favourable conditions extractions carried out as described above give xanthoaphin-*fb* in amounts greater than half of the crude aphin mixture. On the other hand, if preserved insects are used it is very difficult to isolate pure xanthoaphin-*fb* and in such cases it was usually better to employ a modified procedure, as described later, and to proceed directly to the isolation of the chrysoaphin and erythroaphin.

Chrysoaphin-fb.—The combined ether–carbon tetrachloride mother-liquors (40—60 c.c.) from the separation and crystallisation of the xanthoaphin-*fb* in the above experiment were heated under reflux with chloroform (20 c.c.; not specially purified and therefore slightly acidic) until the characteristic 4300-A. line in the visible-light absorption spectrum of the xanthoaphin could no longer be detected with the hand-spectroscope and was replaced by the 4560-A. band of the chrysoaphin. The solution was now concentrated until crystallisation began and then set aside for a short time. *Chrysoaphin*-fb (0·2—0·3 g.)

separated as minute orange crystals. Recrystallised from an acid-free mixture of chloroform and carbon tetrachloride, the substance had no definite m. p. but decomposed with darkening when heated above 250° (Found, in material dried at 60°/0·01 mm. for 14 hours: C, 68·0, 68·4, 68·2; H, 5·2, 4·8, 4·8; active H, 0·57. $C_{30}H_{24}O_5$ requires C, 67·9; H, 5·0%). Qualitative tests for nitrogen, phosphorus, sulphur, halogens, and methoxyl were negative. Light absorption in chloroform: Maxima at 2680, (3260), 3800, 4020, (4300), and 4800 A.; $E^{1\%}_{1cm.}$ = 685, (101), 250, 454, (102), 190, and 213 respectively.

Chrysoaphin-*fb* is readily soluble in chloroform, acetone, dioxan, ethyl acetate, or pyridine, moderately so in ether, benzene, ethanol, or carbon tetrachloride, and sparingly in light petroleum; it is insoluble in water. Neutral or acidic solutions in organic solvents are yellow and have a blue-green fluorescence which is particularly brilliant when viewed in ultra-violet light. The substance dissolves in aqueous alkali to give a crimson solution with an intense orange fluorescence in ultra-violet light. The solid pigment itself has a fine orange fluorescence in ultra-violet light. Chrysoaphin-*fb* is converted into erythroaphin-*fb* on being heated with acids.

Erythroaphin-fb.—The combined mother-liquors from the chrysoaphin-*fb* preparation described above were evaporated under reduced pressure, the residue taken up in chloroform (50 c.c.), and formic acid (5 c.c.; anhydrous) added. The mixture was heated under reflux for 30 minutes, by which time examination of the solution with a hand-spectroscope revealed only the characteristic visible-light absorption bands of erythroaphin-*fb*. Most of the solvent was removed by distillation, warm ethanol (30 c.c.) was added, and the solution concentrated until crystallisation set in. Set aside overnight, *erythroaphin*-fb had separated as small deep-carmine-red needles (0·1 — 0·15 g.); for analysis it was recrystallised several times from chloroform–ethanol [Found, in material dried at 60°/0·01 mm. for 12 hours: C, 70·5, 70·6; H, 4·8, 4·6; active H, 0·64; *C*-CH_3 (Kuhn–Roth), 12·4. $C_{30}H_{24}O_4$ requires C, 70·6; H, 4·4. $C_{30}H_{24}O_5$ requires C, 70·3; H, 4·7%). Erythroaphin-*fb* contains no halogens, nitrogen, phosphorus, sulphur, or methoxyl, and it has no definite m. p., charring and decomposing above 250°. Light absorption in chloroform: Maxima at 2670, 4210, 4465, 4850, 5205, 5600, and 5980 A.; $E^{1\%}_{1cm.}$ = 586, 550, 721, 115, 244, 375, and 165 respectively.

Erythroaphin-*fb* is moderately soluble in chloroform or carbon tetrachloride, somewhat less so in pyridine, acetone, benzene, dioxan, ether, acetic acid, or acetic anhydride; it is very sparingly soluble in ethanol or ethyl acetate and quite insoluble in water. Neutral or acid solutions in organic solvents are red with an orange-red fluorescence which is intense in ultra-violet light. With sodium hydroxide it gives deep-green solutions with a ruby-red fluorescence visible in ultra-violet light. Although neither sodium carbonate nor hydrogen carbonate will extract erythroaphin-*fb* from its solutions in benzene or chloroform, sodium carbonate, but not hydrogen carbonate, will extract it from ether; again, if the pigment is first dissolved in a little acetone, ethanol, or dioxan, addition of either sodium carbonate or hydrogen carbonate will give the characteristic green solutions of the alkali salt, although neither of them in aqueous solution will dissolve the solid pigment. Erythroaphin-*fb* gives a red solution in concentrated sulphuric acid and with acetic anhydride containing a drop of sulphuric acid the initially red solution passes rapidly through green to blue and acquires a strong red fluorescence (*cf.* Blount, *loc. cit.*, on the same reaction with strobinin). Hydrogenation of the pigment (22·8 mg.) in dioxan solution with Adams's catalyst proceeded with uptake of 1·12 mols. of hydrogen (1·19 c.c. at 15°/754 mm.) calculated on a formula $C_{30}H_{24}O_5$, giving a pale brown solution with an intense green fluorescence. On exposure of the reduced solution to air it was rapidly re-oxidised, yielding the original erythroaphin-*fb*. A similar reversible reduction occurred with sodium dithionite.

Modified Extraction Procedure for Preserved Insects.—Since insects which have been preserved in cold storage are useless for preparation of protoaphin and since the isolation of the xanthoaphin was difficult, at any rate in the case of *A. fabæ*, a modified method of extraction has usually been employed in which only chrysoaphin-*fb* and erythroaphin-*fb* were isolated; the yields obtained varied considerably from batch to batch, as indeed they also did with different batches of fresh insects.

The preserved aphids (100 g.) were thoroughly extracted with acetone by the method described above in the preparation of xanthoaphin-*fb*, but the removal of fat by freezing was usually omitted. Any insoluble material was carefully removed before proceeding further, however, in order to avoid undue emulsification in the extraction of the aqueous-acetone solution with light petroleum (b. p. 40—60°; 3 × 250 c.c.). Evaporation of the orange-red petroleum extract left a viscous red oil which was freed from residual acetone under reduced pressure at room temperature. On boiling this oil with a small amount of light petroleum (b. p. 40—60°; 50 c.c.) for 10 minutes most of the fat was removed with little loss of colouring matter. The residue (0·4—0·5 g.), now a granular red powder, was washed with light petroleum and dissolved in chloroform (20 c.c.), carbon tetrachloride (50 c.c.) was added, and the solution concentrated until crystallisation set in. On cooling chrysoaphin-*fb* (75—150 mg.) separated. Erythroaphin-*fb* (50—100 mg.) was obtained from the chrysoaphin-*fb* mother-liquors by treatment with formic acid and working up as described above.

Enzymic Conversion of Protoaphin-fb into the Fluorescent Derived Aphins.—In the presence of a purified enzyme preparation, crushed insects were employed to bring about the conversion. A control experiment was first carried out in which preserved insects (10 g.) were crushed with water (2 c.c.), and the mixture set aside at room temperature for 16 hours and then ground with Hyflo Supercel (0·5 g.) and acetone (20 c.c.). The mixture was filtered and the residue thrice re-extracted in the same way with aqueous acetone (80%; 3 × 20 c.c.). The combined filtrates were extracted with light petroleum (b. p. 40—60°; 3 × 40 c.c.), and the extract was filtered and evaporated under reduced pressure. Fat was removed from the residue by digestion with light petroleum (25 c.c.), and the insoluble mixture of aphins was collected on a sintered-glass funnel, dried, and weighed. The result obtained gave an estimate of the weight of fluorescent aphins derived from the insects used. In subsequent experiments using varying amounts of insects, a weighed amount (*ca.* 60 mg.) of pure protoaphin-*fb* was dissolved in aqueous sodium hydroxide (N./100), the pH was adjusted to 5·8—6·2 by hydrochloric acid (*ca.* 5·6 c.c. of N./100), and the solution added to the insects about to be crushed; subsequent operations were carried out as above. It was found that the results were not materially affected by varying the amount of water used in the first

crushing, but there was some variation according to the length of time the crushed insects were kept before extraction with acetone. For this reason, 18 hours was used as a standard time in the experiments recorded in the accompanying table. It is evident that one aphid contains enough enzyme to convert many times its own content of protoaphin-*fb* into the fluorescent aphins.

Wt. of insects (g.).	Wt. of added protoaphin-*fb* (mg.).	Total yield of aphins (mg.).	Wt. of aphins derived from insects (mg.).	Wt. of aphins derived from protoaphin-*fb* (mg.).
10	—	40·8	40·8	—
0·504	60·1	41·0	2·0	39·0
0·35	60·4	33·6	1·4	32·2
0·25	60·5	32·7	1·0	31·7

Diacetylerythroaphin-fb.—(*a*) *From erythroaphin*-fb. Acetylpyridinium chloride was prepared as a white semi-solid mass by dropwise addition of acetyl chloride (2 c.c.) to pure pyridine (5 c.c.) with shaking and external cooling. Erythroaphin-*fb* (200 mg.) dissolved in ice-cold pyridine (100 c.c.) was now added rapidly and the mixture stirred for 15 minutes and then allowed to come to room temperature; the initially red solution changed during this operation to a bright yellow semi-solid suspension. An equal volume of benzene was added, the mixture poured on ice, and the benzene layer washed thoroughly with water, hydrochloric acid, and again water, dried, and evaporated under reduced pressure. The resinous residue was dissolved in hot ethanol, and the solution concentrated to incipient crystallisation. On cooling, *diacetylerythroaphin*-fb separated as mustard-yellow needles. After two further recrystallisations from ethanol by a similar procedure the pure substance (190 mg.) melted with decomposition at 245—250° after previous darkening (Found: C, 68·5; 68·3; H, 4·5, 4·5; *O*-acetyl, 13·8, 14·2. $C_{36}H_{30}O_8(CO{\cdot}CH_3)_2$ requires C, 68·7; H, 4·4; *O*-acetyl, 14·5. $C_{36}H_{30}O_8(CO{\cdot}CH_3)_2$ requires C, 68·6; H, 4·7; *O*-acetyl, 14·4%). Light absorption in ethanol: Maxima at 2560, 3300, 3470, and 4245 A.; $E^{1\%}_{1cm.}$ = 428, 217, 167, and 566 respectively. Molecular weight by the freezing-point method in ethylene dibromide, 534 ($C_{44}H_{38}O_{10}$ requires *M*, 596).

Diacetylerythroaphin-*fb* appears to be dimorphous, since it was obtained on occasion as red prisms which were not closely examined but changed to the normal yellow form on recrystallisation. It is soluble in most of the common organic solvents with the exception of light petroleum, in which it is very sparingly soluble. Its yellowish-orange solutions in organic solvents fluoresce orange in ultra-violet light, and it is not extracted from such solutions by aqueous sodium hydroxide. Hydrolysis with ethanolic alkali yields erythroaphin-*fb*. Reduction with sodium dithionite or with hydrogen in presence of a platinum catalyst yields (in solution) a yellow product, rapidly re-oxidised to the original compound on exposure to air. Quantitative hydrogenation showed that the uptake of hydrogen during this reduction corresponds to 1 mol.

(*b*) *From chrysoaphin*-fb. Chrysoaphin-*fb* (108 mg.) was dissolved in cold dry pyridine (4 c.c.), acetic anhydride (4 c.c.) added, and the mixture kept in a stoppered flask for 12 hours at room temperature with occasional shaking. Benzene (100 c.c.) was added and the mixture washed with water (3 × 100 c.c.), dilute hydrochloric acid, and again with water. Dried and evaporated, the benzene layer yielded a red gum, which on dissolution in ethanol followed by concentration of the solution furnished yellow needles of diacetylerythroaphin-*fb* (57 mg.), identical with the product obtained by method (*a*) above (Found: C, 68·7, 68·7; H, 4·8, 4·6; *O*-acetyl, 14·6%).

Tetra-acetyldihydroerythroaphin-fb.—Acetic anhydride (2 c.c.) and anhydrous sodium acetate (20 mg.) were added to a solution of erythroaphin-*fb* (28 mg.) in dioxan (2 c.c.), and the whole was shaken with hydrogen at room temperature and atmospheric pressure in presence of Adams's platinum catalyst; hydrogen uptake (1·35 c.c., 1·1 mols.) was complete in 18 minutes. The catalyst was separated, an equal volume of chloroform added, and the solution washed with dilute aqueous sodium carbonate. The chloroform layer was dried and concentrated to small bulk (5 c.c.), and hot ethanol (20 c.c.) added. The filtered solution was then concentrated until crystallisation set in and was set aside to cool. Recrystallisation of the product in the same way gave *tetra-acetyldihydroerythroaphin*-fb (28 mg.) as orange needles which charred but did not melt at <320°. The same product was obtained from diacetylerythroaphin-*fb* by hydrogenation of a solution in acetic anhydride using Adams's platinum catalyst followed by removal of the solvent, treatment with ethanol, evaporation, and crystallisation of the product as above described (Found: C, 66·6, 66·6, 66·8; H, 4·7, 4·9, 4·9; *O*-acetyl, 24·4, 25·3. $C_{36}H_{30}O_8(CO{\cdot}CH_3)_4$ requires C, 67·0; H, 4·7; *O*-acetyl, 25·3. $C_{36}H_{30}O_8(CO{\cdot}CH_3)_4$ requires C, 66·8; H, 5·0; *O*-acetyl, 25·2%). Molecular-weight determination in ethylene dibromide by the cryoscopic method gave a value 740 ($C_{52}H_{46}O_{12}$ requires *M*, 682); the difficulty encountered throughout the aphin series in obtaining consistent values for molecular weights by the common methods leads us to regard this figure as of qualitative rather than quantitative value. The compound is soluble in chloroform (although solutions appear to decompose on storage), moderately soluble in benzene, and sparingly so in ethanol. The yellow solutions in organic solvents exhibit an intense green fluorescence in ultra-violet light. Tetra-acetyldihydroerythroaphin-*fb* is not extracted from such solutions by aqueous sodium hydroxide, nor is it reducible with sodium dithionite. Light absorption in ethanol containing 5% of chloroform: Maxima at 2520, 2785, (3400), 3560, (3865), 4110, 4350, and 4955 A.; $E^{1\%}_{1cm.}$ = 221, 547, (19), 21, (16), 43, 134, 322, and 443 respectively.

Dibenzoylerythroaphin-fb.—Erythroaphin-*fb* (23 mg.) was shaken with pyridine (4 c.c.), benzoyl chloride (0·2 c.c.), and a small crystal of benzoic acid for 15 hours, then warmed to 50° for a few minutes, and evaporated under reduced pressure. The solid residue was dissolved in ether–benzene (1 : 1), and the solution washed with hydrochloric acid, then with sodium hydrogen carbonate, and finally with water before drying (Na_2SO_4). The solution was evaporated, the residue dissolved in hot ethanol, and water added until a cloudiness appeared. On cooling, *dibenzoylerythroaphin*-fb separated as a light-brown amorphous powder (Found: C, 73·1; H, 4·4. $C_{44}H_{30}O_{10}$ requires C, 73·3; H, 4·5%). Molecular-weight determination by the cryoscopic method in ethylene dibromide gave a value 728, but ebullioscopic methods in chloroform gave inconsistent results ($C_{44}H_{30}O_{10}$ requires *M*, 720).

Nitric Acid Oxidation of Erythroaphin-fb.—Erythroaphin-*fb* (100·6 mg.) was heated on the steam-bath with concentrated nitric acid (4 c.c.) until evolution of brown fumes had almost ceased (2 hours), and the pale brownish solution was evaporated to dryness. The residue was again heated with nitric acid (3 c.c.) for 1 hour and then once more evaporated to dryness, and the residue boiled with water (3 c.c.) for 1 hour. Evaporation of the aqueous solution gave a semi-solid mass which was dissolved in methanol (5 c.c.) and treated with excess of ethereal diazomethane. The mixture was set aside overnight and then evaporated. The solid residue was dissolved in a mixture of benzene (2·5 c.c.) and n-pentane (2·5 c.c.) and put on a column of neutral alumina (3 g.). The column was washed with the same solvent and then eluted by washing with benzene containing increasing amounts of chloroform. The main bulk of product was located in the benzene–20% chloroform (30 c.c.; wt. of eluate 5·6 mg.; m. p. 183—184°) and benzene–40% chloroform (30 c.c.; wt. of eluate 9·2 mg.; m. p. 184—185°) washings. The material from these two fractions was combined, re-chromatographed in the same way, and furnished hexamethyl mellitate (13·8 mg.), m. p. 184—185°, unchanged by recrystallisation from aqueous methanol (Found: C, 51·1; H, 4·3. Calc. for $C_{18}H_{18}O_{12}$: C, 50·7; H, 4·3%). The m. p. of the ester was not depressed on admixture with authentic hexamethyl mellitate (m. p. 187°).

The benzene–75% chloroform washings (55 c.c.) of the first chromatogram above gave a crystalline material (5·6 mg.; m. p. 125—150°) which was probably impure hexamethyl mellitate, and washing the column finally with chloroform and methanol gave a resinous material (10 mg.) which was not identified.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 3rd*, 1949.]

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95. *Colouring Matters of the Aphididæ. Part III. Colouring Matters from* Tuberolachnus salignus.

By H. DUEWELL, A. W. JOHNSON, S. F. MACDONALD, and A. R. TODD.

The four aphin colouring matters *protoaphin-sl*, *xanthoaphin-sl*, *chrysoaphin-sl*, and *erythroaphin-sl* have been isolated from the willow-tree aphid, *Tuberolachnus salignus*. Although in most respects the aphins-*sl* are very similar in physical and chemical properties to the aphins-*fb*, the differences between them are sufficiently marked to warrant the conclusion that the pigments of the two series are not identical. A method for the purification of erythroaphins, depending on partition between chloroform and sulphuric acid of varying strengths, has been developed. Erythroaphin-*sl* has been converted into a *diacetyl* and a *tetra-acetyldihydro*-derivative, and from the products of its oxidation with nitric acid mellitic acid has been isolated.

PARALLEL with the investigation of the colouring matters of *A. fabæ* already described (Human, Johnson, MacDonald, and Todd, preceding paper) a study has been made of the large brown aphid, *Tuberolachnus salignus* (Gmelin). This insect parasitises willow trees, especially the white willow, *Salix alba*, on which it forms large colonies on the underside of the branches from late summer until the first severe frosts. It is a very suitable aphid for chemical study as its colonies are usually free of foreign insects, its pigment content (up to 2% of the live weight) is very high, and it is large enough to be easily dislodged from the willow branches by gentle tapping, so that it is readily obtained alive and undamaged without resort to the washing processes necessary with *A. fabæ* and other species. From *T. salignus* we have obtained a series of colouring matters exactly analogous to those from *A. fabæ*. Following the system of nomenclature which has been laid down elsewhere (Duewell, Human, Johnson, MacDonald, and Todd, *Nature*, **1948**, **162**, 759), the *T. salignus* pigments isolated have been named *protoaphin*-sl, *xanthoaphin*-sl, *chrysoaphin*-sl, and *erythroaphin*-sl. Although very similar in many of their properties to the corresponding *A. fabæ* pigments, they are apparently not identical with them.

As in the case of *A. fabæ*, the living insects contain protoaphin-*sl* which can be obtained only if the insects are killed by a method (*e.g.*, heating) which simultaneously inactivates or destroys the enzyme system which brings about the protoaphin–xanthoaphin conversion. Preliminary fermentation of dead insects gives material from which xanthoaphin-*sl*, chrysoaphin-*sl*, and erythroaphin-*sl* in variable amount can be obtained. The pure aphins-*sl* undergo the same interconversions as do the aphins-*fb*, and the methods of extraction and isolation used for them

are generally similar to those used for the aphins-*fb*. The virtual absence of any green pigment similar to that which occurs in extracts of *A. fabæ* makes it easier to observe colour changes in the earlier stages of the extractions and differences in detail arise from the greater stability of xanthoaphin-*sl* as compared with xanthoaphin-*fb*. Thus, although specimens of *T. saligna* which have been long in storage or have been improperly fermented require extraction with acetone to obtain the mixture of fluorescent aphins, fresh insects which have been carefully fermented at pH 6·5 yield xanthoaphin-*sl* almost exclusively, and this compound can be directly extracted with ether. The isolation of all the erythroaphin-*sl* present in insect extracts from which the xanthoaphin and chrysoaphin have been largely removed presents difficulty owing to the accompanying fatty material and other impurities. This difficulty has been overcome by the discovery that the erythroaphin can be quantitatively extracted from chloroform by 72% sulphuric acid, and from 64% sulphuric acid by chloroform. Provided that the chloroform used is free from alcohols and chlorine this method gives excellent results and it can be applied not merely to erythroaphin-*sl* but also to the erythroaphins of *A. fabæ* and other species. It cannot, of course, be applied to either xanthoaphins or chrysoaphins, since these are converted at once into erythroaphins under such acid conditions. Partition between organic solvents and strong acids has been employed in the purification of several natural colouring matters, *e.g.*, porphyrins (Willstätter and Stoll, "Untersuchungen über Chlorophyll," Berlin, 1913, p. 263), stercobilin (Watson, *Z. physiol. Chem.*, 1935, **233**, 39), and azulenes (Plattner, Heilbronner, and Weber, *Helv. Chim. Acta*, 1949, **32**, 574) and might well find more general application; we have found, for example, that it is possible to separate mixtures of hydroxyanthraquinones, *e.g.*, catenarin and cynodontin, by partition between chloroform and 80% sulphuric acid.

In colour and general reactions the four aphins-*sl* are very similar to the corresponding aphins-*fb* (preceding paper). In visible and ultra-violet absorption and in fluorescence they are virtually indistinguishable. Despite these facts, the two series do not appear to be identical. There are differences in solubility, behaviour on heating, and crystalline form, and *X*-ray diffraction photographs of the aphins-*sl* show definite differences from those of the corresponding aphins-*fb*. According to observations made by Dr. N. Sheppard, differences also occur in the infra-red absorption spectra. The most striking difference however is found in the xanthoaphins. While the chrysoaphins and erythroaphins of the two series give analytical values indicating that they might well have the same molecular formulæ, the two xanthoaphins are markedly different in their carbon content; moreover, in the course of experimental work xanthoaphin-*sl* has consistently seemed more stable than its counterpart from *A. fabæ*.

As in the *A. fabæ* series, most of the chemical work so far carried out has been on erythroaphin-*sl*. This pigment we believe has a formula $C_{30}H_{34}O_9$, the evidence being analogous to that adduced in the case of erythroaphin-*fb* (preceding paper). Molecular-weight determinations by ebullioscopic methods gave variable results between 252 and 615 and *X*-ray crystallographic examination gave a value of 534 $\pm$ 5%, assuming 12 molecules per unit cell. Erythroaphin-*sl* is evidently quinonoid in nature and undergoes reversible reduction with sodium dithionite or with hydrogen in presence of a platinum catalyst, 1 mole of hydrogen being absorbed on the basis of a C_{30} formula for the pigment. Acetylation yields *diacetylerythroaphin*-sl and reductive acetylation *tetra-acetyldihydroerythroaphin*-sl.

Of the oxygen atoms in the erythroaphin-*sl* molecule, two are present in a quinone grouping and two in hydroxy-groups, which are probably phenolic in nature since the pigment can be extracted from organic solvents by aqueous sodium hydroxide giving a bright green precipitate. The function of the remaining four oxygen atoms is unknown. There is no evidence of carboxy-groups since neither diacetylerythroaphin-*sl* nor tetra-acetyldihydroerythroaphin-*sl* can be extracted from chloroform solution with dilute alkali. On the other hand, certain observations suggest the possibility that one or more lactonic or other latent acidic groups may be present. When a little sodium hydroxide is added to a solution of diacetylerythroaphin-*sl* in aqueous acetone, the colour changes from brownish-orange to green; this change does not involve deacetylation, since, if the green solution is quickly acidified, the original diacetylerythroaphin-*sl* is recovered unchanged. Similar treatment of tetra-acetyldihydroerythroaphin-*sl* with alkali under conditions which do not remove the acetyl groups gives a colour change yellow-red. Again, treatment of erythroaphin-*sl* in ethanol–dioxan solution with anhydrous hydrogen chloride gives a deep-green product, and addition of ethanol to the red solution of erythroaphin-*sl* in concentrated sulphuric acid causes a colour change to green.

In its behaviour towards bases erythroaphin-*sl* shows properties analogous to those described by Scholl (*Ber.*, 1941, **74**, 1129, 1171, 1182) in the hydroxyanthraquinone group. In

dry pyridine it dissolves to a red solution, but in aqueous pyridine its solutions are green. Addition of excess of dry pyridine to the aqueous solution brings about a change from green to red. In general, erythroaphin-*sl* dissolves in tertiary bases to give red solutions which become green on addition of water, whereas in many primary and secondary amines (aniline is an exception) the solutions are green and are unaffected by water. We have also observed that hypericin behaves in a similar manner with bases.

As to the nature of the nucleus in erythroaphin-*sl* little is known. It evidently contains a fully substituted aromatic ring, since oxidation with nitric acid gives mellitic acid, just as it does with erythroaphin-*fb*. Other methods of oxidation did not yield identifiable products in preliminary experiments and zinc-dust fusions or distillations gave fluorescent oils, evidently mixtures of hydrocarbons, from which no solid products were isolated.

Very little work has yet been done on the other aphins from *T. saligna* and it is not yet possible to assign molecular formulæ to them with any certainty. On the assumptions that erythroaphin-*sl* has a molecular weight of 512 and that 1 mol. of xanthoaphin gives rise to 1 mol. of chrysoaphin and this in turn to 1 mol. of erythroaphin, the yields of the last-named pigment obtained in conversion reactions suggest that chrysoaphin-*sl* should have a molecular weight of > 584, which would not conflict with a formula such as $C_{30}H_{32}O_9$. On the same basis, xanthoaphin-*sl* should have a molecular weight of > 615 but it must be admitted that the surprisingly low hydrogen content (4·5%) found on elementary analysis makes it difficult to advance a formula bearing a simple relation to those of the others, as was possible in the case of the *A. fabæ* series (Human *et al.*, *loc. cit.*). Further examination of xanthoaphin-*sl* is clearly needed before any conclusions can be drawn. Since protoaphin-*sl* has been more superficially examined than the other *T. saligna* pigments, it is difficult to say whether the slightly lower carbon content observed as compared with protoaphin-*fb* is significant. It is at any rate clear that the pigments of the two series are very closely related to one another.

Experimental.

Unless otherwise stated, light petroleum refers to the fraction, b. p. 40—60°.

Collection of Insects.—Willow branches infected with *T. saligna* were carefully sawn into convenient lengths for handling and the insects dislodged from the undersides by gentle tapping and collected on Cellophane sheets. If not worked up immediately, the aphids so obtained were stored below −10° in glass bottles. Stored insects could not be used for the preparation of the protoaphin and were also unsatisfactory as raw material for the pure xanthoaphin. In the 1947 season some 960 g. of insects were collected and in 1948 *ca.* 450 g.; although by the final extraction methods up to 2% of mixed pigments can be isolated, losses were heavy in the earlier stages of our investigations and the total quantity of mixed aphins isolated was 11·9 g. Further losses were involved in separating the individual aphins from the mixture.

Protoaphin-sl.—The aphids (5 g.) were killed by plunging them into water at 80° for one minute. The dead insects were collected, washed with a little aqueous acetone (60%), and then extracted with the same solvent by grinding in a Waring Blendor for a few minutes. The mass was filtered and the filtrate (50 c.c.) thrice extracted with light petroleum, the volume being brought up to 50 c.c. after each extraction by addition of acetone. The filtered extract was concentrated until it began to foam, whereupon it was cooled and shaken with active charcoal (Darco G. 60; 0·25 g. and 0·5 g. in successive lots). Elution of the second lot of charcoal (0·5 g.) with aqueous acetone (75%), followed by concentration to small bulk and prolonged cooling, yielded *protoaphin-sl* (30 mg.) as small tan-coloured needles (Found: C, 54·8; 54·7; H, 5·8, 6·2%). No crystalline material was obtained from the elution of the first lot of charcoal. Protoaphin-*sl*, which has not been very closely studied as yet, is similar to protoaphin-*fb* (preceding paper) in all its properties. Its solutions are yellow in neutral or acidic conditions and purple-red in alkaline. Addition of fresh crushed aphids to an aqueous solution of protoaphin-*sl* buffered to pH 6·5 causes rapid conversion into xanthoaphin-*sl*.

Xanthoaphin-sl.—*Method* 1. Freshly collected *T. saligna* (100 g.) suspended in phosphate buffer (250 c.c.; pH 6·5) were pulped in a Waring Blendor and the insect sludge kept for 3 hours at room temperature before removal of fat by extraction with cold carbon tetrachloride (2 × 100 c.c.). The mixture of fluorescent aphins was then extracted with ether (5 × 100 c.c.), and the solvent was slowly distilled from the combined ethereal extracts. After the volume had been reduced to 150 c.c. it was maintained by slow addition of carbon tetrachloride (90 c.c.). The distillation of the resulting mixture was continued until the temperature of the vapour was 72°, whereupon the solution was set aside at room temperature for several hours. The *xanthoaphin-sl* (774 mg., 0·8%) which separated was purified by extraction from a thimble with acid-free ether, concentration to small bulk, and initiation of crystallisation by addition of pure carbon tetrachloride. It then formed bright yellow plates which had a yellow fluorescence in ultra-violet light and on heating darkened from *ca.* 170° and finally melted at 203—204° (Found, in material dried at room temperature: C, 59·9, 59·4, 59·6, 59·3; H, 4·4, 4·6, 4·3, 4·4. $C_{30}H_{34}O_{14}$ requires C, 59·1; H, 4·3%).

Because of the ease of conversion into chrysoaphin-*sl*, it is preferable to recrystallise not more than *ca.* 400 mg. at one time, and to store the solid pigment in the dark. Xanthoaphin-*sl* is very soluble in pyridine, acetone, ethanol, or ethyl acetate, moderately so in chloroform or ether, and sparingly soluble in cold benzene; it is very sparingly soluble in light petroleum or carbon tetrachloride. Solutions in

organic solvents are yellow with a strong bluish-green fluorescence which is intensified in ultra-violet light. Alkaline solutions are pink with a green fluorescence when freshly prepared but, when kept, quickly change through crimson to green owing to progressive change to chrysoaphin-*sl* and erythroaphin-*sl*. Neutral solutions are more stable but the same changes occur on prolonged heating or if they are made acid. Light absorption in chloroform: Maxima at 2590, 2815, 3600, 3800, 4070, 4310, and 4590 A.; $E^{1\%}_{1cm.}$ = 821, 880, 196, 394, 118, 189, and 205 respectively. The bands at 4310 and 4590 A. are easily detected with a hand spectroscope.

Method 2. Fresh *T. saligena* (80 g.) were suspended in phosphate buffer (200 c.c.; pH 6·5) and pulped in a Waring Blendor, giving a deep purplish-red sludge, which was left at room temperature for 1 hour, the colour changing to greenish-yellow. The sludge was extracted with light petroleum (200 c.c.) which removed most of the fat, together with a little of the pigment. Acetone (200 c.c.) was added to the insect sludge, the whole thoroughly stirred, and solid material removed by centrifugation; this solid was re-extracted in the same way with aqueous acetone (5 × 200 c.c. of 80%). The combined acetone extracts were then repeatedly shaken with light petroleum (11 × 200 c.c.), and the combined petroleum layers evaporated under reduced pressure (temp. >20°). The residue was diluted with light petroleum and again concentrated to small bulk (40 c.c.). The mixed aphins separated as a light-orange granular precipitate (1·4—1·7 g.) which was collected, washed with light petroleum, and dried at room temperature. The colouring matter remaining in the mother-liquor was later converted into erythroaphin-*sl* by treatment with formic acid (see below). The crude solid pigments (400 mg. at one time) were dissolved in acid-free ether by extraction from a thimble and the solution slowly distilled, carbon tetrachloride being added continuously until crystallisation set in. On cooling xanthoaphin-*sl* separated and was recrystallised from ether–carbon tetrachloride. In favourable cases the yield was about 40% of the weight of the crude pigments.

Chrysoaphin-sl.—This pigment was usually isolated from the mother-liquors of the xanthoaphin-*sl* prepared by Method 1 or 2 above, by further concentration and replacement of ether by carbon tetrachloride. The crude chrysoaphin so obtained (*e.g.*, 493 mg., 0·5% from 100 g. of insects by Method 1) was dissolved in chloroform and shaken with aqueous formic acid (10%) until the 4310-A. band of xanthoaphin-*sl* was no longer visible with the hand-spectroscope. The chloroform solution was then washed with water, dried, and evaporated. The residue was triturated with light petroleum and the granular *chrysoaphin*-sl collected and recrystallised from ether by extraction from a thimble followed by concentration of the solution. It formed small orange needles which fluoresce orange in ultra-violet light, m. p. 235—239° (decomp. with previous darkening) (Found, in material dried at 60°/0·01 mm. for 6 hours: C, 68·3, 68·2, 68·4; H, 5·0, 4·7, 5·0. $C_{30}H_{44}O_3$ requires C, 67·9; H, 4·9. $C_{32}H_{44}O_{10}$ requires C, 68·4; H, 5·0%). Light absorption in chloroform: Maxima at 3210, 3820, 4040, 4565, and 4850 A.; $E^{1\%}_{1cm.}$ = 195, 419, 553, 206, and 253 respectively. The bands at 4850 and 4565 A. are readily detected with a hand-spectroscope. Chrysoaphin-*sl* is very soluble in pyridine, soluble in chloroform, acetone, ethyl acetate, or benzene, sparingly soluble in carbon tetrachloride, ether, or ethanol and virtually insoluble in light petroleum. Solutions in organic solvents are yellow with a green fluorescence which in ultra-violet light becomes intense yellowish-green. Alkaline solutions are crimson but become green as conversion into a salt of erythroaphin-*sl* proceeds.

Erythroaphin-sl.—(i) *From chrysoaphin*-sl *mother-liquors.* The mother-liquors from the above chrysoaphin-*sl* preparation were evaporated, and the residue was dissolved in ethyl acetate (120 c.c.). Formic acid (20 c.c. of 85%) was added and the solution heated on the steam-bath for 5 minutes. On cooling, *erythroaphin*-sl (691 mg., 0·7% from 100 g. of insects) separated as dark red needles, m. p. 250—252° (decomp. with previous darkening), and was recrystallised from ether (extraction in a thimble) or from chloroform–ethanol (Found, in material dried at 60°/0·01 mm. for 12 hours: C, 70·2, 70·1, 70·1; H, 4·3, 4·3, 4·5. $C_{30}H_{44}O_3$ requires C, 70·3; H, 4·7. $C_{32}H_{44}O_4$ requires C, 70·6; H, 4·4%). Light absorption: (1) *In chloroform.* Maxima at 2555, 3195, 3335, 4215, 4470, 4855, 5200, 5600, and 5860 A.; log $\varepsilon_{max.}$ 4·57, 3·65, 3·65, 4·49, 4·61, 3·77, 4·11, 4·30, and 3·90 respectively. (2) *In concentrated sulphuric acid.* Maxima at 2330, 2730, 2900, 4620, 5200, and 5680 A.; log $\varepsilon_{max.}$ 4·66, 4·35, 4·27, 4·46, 4·28, and 4·55 respectively. (3) *In dioxan–N/100-sodium hydroxide* (1 : 1). Maxima at 2880, 4220, 4480, 5750, and 6215 A.; log $\varepsilon_{max.}$ 4·70, 4·47, 4·56, 4·18, and 4·45 respectively.

Erythroaphin-*sl* is very soluble in pyridine or chloroform, soluble in carbon tetrachloride, acetone, or benzene, and sparingly soluble in ethyl acetate, ethanol, or light petroleum. Solutions in organic solvents are deep red with an orange fluorescence which is intense when viewed in ultra-violet light. The solid pigment has a dull red fluorescence in ultra-violet light. Solutions in sulphuric acid are red and show no fluorescence. With acetic anhydride containing a drop of sulphuric acid the solution passes through green to pure blue with an intense red fluorescence. Extraction of chloroform solutions of erythroaphin-*sl* with aqueous sodium hydroxide yields the insoluble green sodium salt at the interface.

Erythroaphin-*sl* is reversibly reduced by sodium dithionite or by catalytic hydrogenation, the reduced form being rapidly reoxidised in air. Quantitative hydrogenation with a platinum catalyst gave values of 487 and 495 for the molecular weight, assuming one quinone grouping per molecule. Ebullioscopic methods gave variable results (from 252—615) but *X*-ray crystallographic examination gave *M* 534 ± 5%, assuming 12 mols. per unit cell ($C_{30}H_{44}O_3$ requires *M*, 512).

(ii) *From crystallins chrysoaphin*-sl *or xanthoaphin*-sl. Chrysoaphin-*sl* (50 mg.) was dissolved in ethanol (50 c.c.) and concentrated sulphuric acid (0·3 c.c.) was added with shaking. The solution was set aside for 5½ hours and the erythroaphin-*sl* which separated was collected, washed with ethanol and light petroleum, and dried (yield, 43·7 mg.). Xanthoaphin-*sl* (50·1 mg.) treated in the same way also yielded erythroaphin-*sl* (41·7 mg.). The conversion of either pigment into erythroaphin-*sl* could also be brought about by heating it with ethyl acetate containing formic acid.

On the assumptions that the conversions are unimolecular and that erythroaphin-*sl* has a molecular weight of 512, the yields obtained in the conversions fix an upper limit for the molecular weight of chrysoaphin-*sl* at 584 and for xanthoaphin-*sl* at 615.

Purification of Erythroaphin-sl by Partition.—Crude erythroaphin-*sl* (1·018 g.), dissolved in alcohol-

free chloroform (70 c.c.), was shaken with sulphuric acid (125 c.c.; 74%), whereupon the pigment passed into the acid layer. The acid solution was washed with chloroform (50 c.c.), then diluted with sulphuric acid (400 c.c. of 62%), and extracted with chloroform (6 × 50 c.c.); the red pigment passed into the chloroform, leaving a brownish aqueous-acid layer. The chloroform extracts were repeatedly washed with water, dried, and concentrated to small bulk under reduced pressure. Ethanol was added until a turbidity appeared and the mixture was warmed to bring all into solution and set aside overnight, whereupon pure erythroaphin-*sl* separated.

Diacetylerythroaphin-sl.—Erythroaphin-*sl* (398 mg.) was dissolved in cold dry pyridine (50 c.c.), the solution cooled in ice, and acetyl chloride (8 c.c.) added dropwise with vigorous shaking, the temperature being kept below 10°. After the addition of acetyl chloride cooling was no longer necessary and the mixture was kept at room temperature for 15 minutes, by which time the initially red solution had changed to yellow. The solution was poured, with stirring, into ice-water, and the flocculent brown precipitate collected, washed with water, and dried; it then formed a brown amorphous powder (439 mg.). The crude product was extracted from a thimble with hot light petroleum–ether (1 : 1) during 2 hours and the separated material collected; a further quantity was recovered by evaporation of the solution. Further purification was effected by chromatography on a 1 : 1 talc–precipitated silica column (10 g.; 12 × 1·6 cm.). The diacetyl compound (219 mg.) in 50% benzene–light petroleum was brought on to the column and the solution forced through by application of pressure. The column was washed with more solvent until the eluate was colourless and then most of the solvent was removed from the combined eluate. *Diacetylerythroaphin*-sl was then precipitated by the addition of excess of light petroleum, being obtained as a light orange powder. It has been obtained crystalline only on one occasion so far and the analyses and determinations of spectra, etc., have mostly been carried out on amorphous material [Found: C, 68·8, 68·4; H, 4·6, 4·5; *O*-acetyl, 15·2, 13·5, 13·4%; *M* (ebullioscopic in chloroform), 572; (hydrogenation in dioxan over Pt), 593, 596. $C_{26}H_{22}O_9(CO{\cdot}CH_3)_4$ requires C, 68·4; H, 4·7; *O*-acetyl, 14·4%; *M*, 596). Diacetylerythroaphin-*sl* is very soluble in acetone, ethyl acetate, benzene, or pyridine, soluble in ether, alcohol, or methanol, sparingly soluble in light petroleum, and insoluble in water. Light absorption in chloroform (amorphous material): Maxima at 5870, 5360, 4920, 4280, 3490, 3330, and 2560 A.; log $\varepsilon_{max.}$ = 2·80, 3·34, 3·85, 4·55, 3·95, 4·07, and 4·42 respectively.

Tetra-acetyldihydroerythroaphin-sl.—(i) *Reductive acetylation of erythroaphin*-sl. Erythroaphin-*sl* (123 mg.), pure zinc dust (246 mg.), and anhydrous sodium acetate (25 mg.) were suspended in acetic anhydride (5 c.c.), and glacial acetic acid (1 c.c.) was added. The mixture was warmed and gently shaken until solution had been effected, and then heated under gentle reflux for 15 minutes. The reddish solution then showed a green fluorescence, and the completion of the reaction could be conveniently determined by adding a drop of the mixture to chloroform (1 c.c.) and shaking with water. When the chloroform solution stayed yellow, showing absorption bands at 4990 and 4670 A. (hand-spectroscope), and no re-oxidation took place in air, the solid material was separated from the hot reaction mixture, and the residue washed with hot acetic acid. The filtrate and washings were diluted with water, excess of acetic anhydride was hydrolysed, and the pale brown precipitate (151 mg.) separated, washed with water, and dried *in vacuo*. The crude acetyl derivative was dissolved in benzene (20 c.c.) and light petroleum (10 c.c.), and brought on to a 1 : 1 talc–precipitated silica column (10 g.; 11 × 1·6 cm.), and the solution forced through by application of pressure. The column was washed with light petroleum until the eluate was no longer coloured. The benzene addition *compound* of tetra-acetyldihydroerythroaphin-*sl* began to separate from the combined eluates after a few minutes (addition of more light petroleum if necessary), and after 12 hours the golden-yellow crystals of the benzene adduct were collected (123 mg.), m. p. 325° (decomp.). For analysis a sample was re-chromatographed and dried *in vacuo* at 60° (Found: C, 69·8; H, 5·1. $C_{34}H_{34}O_{13}.C_6H_6$ requires C, 69·5; H, 5·3%). The benzene adduct was dissolved in chloroform (2 c.c.), and hot ethanol (25 c.c.) added. After 24 hours the orange platelets of *tetra-acetyldihydroerythroaphin*-sl were separated, washed with ethanol, and dried as above. The product darkened but did not melt below 320° (Found: C, 66·9; H, 5·1. $C_{34}H_{34}O_{13}$ requires C, 66·9; H, 5·0%). The tetra-acetyl compound is very soluble in pyridine and acetone, soluble in ethyl acetate, chloroform, or benzene, sparingly soluble in ether or ethanol, and insoluble in light petroleum. Light absorption in chloroform: Maxima at 2785, 4365, 4650, and 4980 A.; log $\varepsilon_{max.}$ = 4·56, 3·94, 4·30, and 4·43 respectively. Samples of the tetra-acetyl compound tend to deteriorate on storage, with the production of amorphous impurities, which, however, can be conveniently removed by chromatography on talc–precipitated silica columns as outlined above.

(ii) *Catalytic reductive acetylation of erythroaphin*-sl. Erythroaphin-*sl* (200 mg.), acetic anhydride (20 c.c.), anhydrous sodium acetate (50 mg.), and Adams's platinum catalyst (50 mg.) were hydrogenated at atmospheric pressure until no more hydrogen was absorbed. The catalyst was separated from the yellow solution, excess of ethanol added, and the mixture kept overnight. The solvent was removed under reduced pressure, the residue treated with water, and the crude acetyl compound separated, washed with water, and dried (250 mg.). The further purification was similar to that described in method (i). The acetyl compound was dissolved in 50% benzene–light petroleum and twice chromatographed on 1 : 1 talc–precipitated silica to yield the benzene addition product (175 mg.) (Found: C, 69·3; H, 4·9%). Recrystallisation from ethanol–chloroform gave pure tetra-acetyldihydroerythroaphin-*sl* [Found: C, 66·9; H, 4·7; *O*-acetyl, 24·8. Calc. for $C_{26}H_{22}O_9(CO{\cdot}CH_3)_4$: C, 66·9; H, 5·0; *O*-acetyl, 25·2%]. The absorption spectrum of the product was identical with that of the tetra-acetyl compound obtained by method (i). The catalytic reductive acetylation method is best for preparative purposes. In the absence of sodium acetate acetylation was incomplete.

(iii) *Catalytic reductive acetylation of diacetylerythroaphin*-sl. Diacetylerythroaphin-*sl* (216 mg.), acetic anhydride (15 c.c.), anhydrous sodium acetate (30 mg.), and Adams's platinum catalyst (50 mg.) were hydrogenated at atmospheric pressure until equilibrium was attained. The catalyst was separated, ethanol (45 c.c.) added, and the mixture kept overnight. The light-brown crystals were removed and a further crop (135 mg.) was obtained by concentration of the mother-liquors and addition of more ethanol. The crude material was purified by chromatography and crystallisation as described above

(Found: C, 66·7; H, 4·8; *O*-acetyl, 25·5%). The identity of the product with the previous preparations was also shown by comparison of the absorption spectra which revealed no differences.

Oxidation of Erythraphin-si with Nitric Acid.—Erythraphin-*si* (98 mg.) was warmed on the steam-bath with nitric acid (3 c.c.), a vigorous reaction setting in with copious evolution of nitrous fumes. The reaction soon subsided and the solution was heated for a further 2 hours. The reaction solution was transferred to a small flask and evaporated at 100° in a stream of air, leaving a pale yellow solid. Nitric acid (2 c.c.) was added, the solution again evaporated to dryness, and the process then repeated twice with water (2 c.c.) in order to remove any excess of nitric acid. The crude oxidation product was treated with excess of ethereal diazomethane, and the methylated material dissolved in benzene and put on a column of neutral alumina (5·4 g.). The chromatogram was washed with benzene, and then with benzene containing increasing amounts of chloroform. Those fractions which were obtained from the washings, up to benzene–40% chloroform, were crystalline (76·7 mg. in all), but the later runnings obtained with higher concentrations of chloroform and with chloroform–methanol mixtures were oily (70·6 mg.) and their nature has not been established. The combined crystalline fractions were re-chromatographed on neutral alumina (2·3 g.) with benzene–light petroleum (1 : 1) as solvent and elution with benzene–light petroleum (3 : 1). Recrystallised from aqueous methanol the product formed silky needles, m. p. 187—188° (Found: C, 50·9, 50·8; H, 4·7, 4·5. Calc. for $C_{12}H_{16}O_{12}$: C, 50·7; H, 4·3%). A mixed m. p. with authentic hexamethyl mellitate (m. p. 187—188°), kindly supplied by Dr. H. C. Howard of the Coal Research Laboratory, Pittsburgh, Pa., showed no depression.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 3rd*, 1949.]

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96. *Acid-catalysed Hydration of Acraldehyde. Kinetics of the Reaction and Isolation of β-Hydroxypropaldehyde.*

By R. H. HALL and E. S. STERN.

A kinetic study of the acid-catalysed hydration of acraldehyde to β-hydroxypropaldehyde (hydracraldehyde; 3-hydroxypropan-1-al) in aqueous sulphuric acid confirms that the reaction is of the first order with respect to acraldehyde. The rate constants are independent of initial acraldehyde concentration, increase with increasing acid concentration, and are strictly proportional to Hammett's acidity function. β-Hydroxypropaldehyde, isolated (in poor yield) from the hydration media and characterised as the 2 : 4-dinitrophenylhydrazone, dimerises spontaneously to 4-hydroxy-3-2′-hydroxyethyl-1 : 3-dioxan, the unsymmetrical structure of which is proved by acetylation and hydrolysis. Representative kinetic experiments on the dehydration of β-hydroxypropaldehyde, using the dimer as starting material, demonstrate the ready reversibility of both the dimerisation of this aldehyde and the hydration of acraldehyde. A reversible mechanism proposed for the hydration of acraldehyde involves, as rate-determining step, the addition of a water molecule to the oxonium ion $CH_2{:}CH{\cdot}CH{:}OH^+$ and the simultaneous redistribution of the charge to give the oxonium ion $^+H_2O{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OH$ which is the conjugate acid of the enol of β-hydroxypropaldehyde.

WITH the ready availability of acraldehyde on a commercial scale (see, *inter alia*, B.P. 569,625, 573,507, 600,454, 625,330; B.P. Appl. 22,712/39; Watson, *Chem. Eng.*, 1947, **54**, No. 12, 107), the preparation of β-hydroxypropaldehyde, an intermediate of great potential value in the solvent or the plasticiser field, has recently received considerable attention.

Although β-hydroxypropaldehyde may be prepared in several ways (cf. Nef, *Annalen*, 1904, **335**, 219; Glattfield and Sander, *J. Amer. Chem. Soc.*, 1921, **43**, 2075; Wohl and Schweitzer, *Ber.*, 1908, **41**, 3603; Stepanow and Schtschukin, *Chem. Zentr.*, 1927, I, 1167), most of the recent work has been concerned with the acid-catalysed hydration of acraldehyde (U.S.P. 2,434,110; German microfilmed reports PB 70,309, Frames 8214—8220; 73,508, Frames 7528—7537; and 19,417; G.P. Appl. D 89,752 IVd, Class o, 1943).

For the catalytic hydration processes described in the literature, conditions seem to be chosen rather arbitrarily and little systematic work appears to have been published in this connection. The kinetic data on the hydration of acraldehyde (Pressman and Lucas, *J. Amer. Chem. Soc.*, 1942, **64**, 1953), which are rather incomplete, are based on experiments with perchloric acid as catalyst and very dilute (about 0·03M.) solutions of acraldehyde, and are not, therefore, directly applicable to preparative work. A detailed kinetic study of the acid-catalysed hydration of acraldehyde was undertaken to provide fuller data, capable of such application, and an insight into the mechanism of the reaction, which has not hitherto been fully elucidated (cf. Hammett, "Physical Organic Chemistry," McGraw-Hill, 1940, p. 293).

In the present work the catalyst used for the hydration of acraldehyde between 20° and 50° was sulphuric acid in the concentration range 0·2—3·8N. The aldehyde concentration range studied was 0·138—2·76M. (*i.e.*, 1—20% v/v). In view of the possible polymerisation of acraldehyde in acid solution, it was decided to follow not only the rate of disappearance of the ethenoid unsaturation (by the bromine absorption method) but also the variations in the concentration of the carbonyl function (by an oximation procedure).

The presence of the acid catalyst, however, introduced large blank values into the analytical determinations of the carbonyl function and accurate values were difficult to obtain. Nevertheless, it was established that during the kinetic runs the aldehyde content of the media remained sensibly constant until after the equilibrium point of the hydration reaction had been reached. Prolonged reaction beyond this point, however, caused a diminution in the aldehyde concentration and it was concluded that a slow polymerisation was then occurring. It was also found that the rate of disappearance of aldehyde during this stage increased with increasing initial acid and acraldehyde concentrations. The fate of the aldehyde group during the polymerisation was not further investigated but it has been stated by Helberger (PB 19,417; FD 4806/47) that 3-formyl-Δ^2-dihydropyran is formed as hydration product. His claim that this is the sole volatile reaction product, however, is invalidated by the isolation of β-hydroxypropaldehyde from hydration media in the course of the present work (see below).

The kinetic data for the hydration of acraldehyde are collected in Tables I and II; the equilibrium concentration of acraldehyde was determined in each case and all kinetic runs were performed in duplicate. The equilibrium position was found to vary with temperature (cf. Pressman and Lucas, *loc. cit.*) and with the aldehyde concentration (Table II), higher conversions being achieved at lower temperatures and higher initial acraldehyde concentration; acid concentration was found to have no appreciable effect on the equilibrium position. The equilibrium constant K was calculated from the equation

$$K = \frac{\text{equilibrium concentration of } \beta\text{-hydroxypropaldehyde}}{\text{equilibrium concentration of acraldehyde}}$$

and the relationship $K = k_1/k_{-1}$ gave the ratio of the first-order rate constants of the forward and the backward reaction.

$$H_2O + CH_2{:}CH{\cdot}CHO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HO{\cdot}CH_2{\cdot}CH_2{\cdot}CHO$$

The sum of these rate constants corresponds to the overall rate constant k determined experimentally and defined (Hammett, *op. cit.*, p. 102) by

$$k = k_1 + k_{-1} = (2{\cdot}3/t) \log x_e/(x_e - x)$$

where x_e is the β-hydroxypropaldehyde concentration at equilibrium and x is that at time t.

TABLE I.

Effect of acid concentration and of temperature.

Initial acraldehyde concn. = 0·690M. throughout; k_1 = first-order rate constant of hydration; k_{-1} = first-order rate constant of dehydration; c_a = acid concentration; $K = k_1/k_{-1}$; H_0 = acidity function (values of Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721).

Temp.	H_2SO_4 concn. (N.).	$10^4(k_1 + k_{-1})$ (min.$^{-1}$).	10^4k_1 (min.$^{-1}$).	10^4k_{-1} (min.$^{-1}$).	Conversion at equilibrium (%).	K.	H_0.	$\log 10^4(k_1 + k_{-1}) + H_0$.	$\frac{10^4(k_1 + k_{-1})}{c_a}$.
20·0°	0·20	4·25	4·06	0·19	95·5	21·2	+1·26	1·88	21·3
20·0	1·00	22·5	21·5	1·0			+0·52	1·87	22·5
20·0	2·00	54·6	52·1	2·5			+0·12	1·86	27·3
20·0	3·80	152	145	7·0			−0·52	1·66	40
30·0	0·20	10·9	10·3	0·62	94·3	16·5	+1·26	2·30	54·5
30·0	1·00	57·8	54·5	3·3			+0·52	2·24	57·8
30·0	2·00	135	127	7·7			+0·12	2·25	67·5
30·0	3·80	350	330	20			−0·52	2·02	92·1
40·0	0·20	24·7	22·7	2·0	92·0	11·5	+1·26	2·65	124
40·0	1·00	133	122	11			+0·52	2·64	133
40·0	2·00	312	287	25			+0·12	2·61	156
40·0	3·80	855	767	68			−0·52	2·41	225
50·0	0·20	60·5	53·9	6·6	89·0	8·1	+1·26	3·04	303
50·0	1·00	305	272	33			+0·52	3·00	305
50·0	1·50	470	418	52			+0·32	2·99	313
50·0	2·00	665	592	73			+0·12	2·94	333

TABLE II.

Effect of acraldehyde concentration.

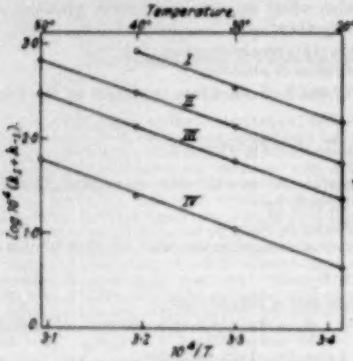
H_2SO_4 concn. is 1·00N. throughout.

Temp.	Initial acraldehyde concn. (M.).	$10^4(k_1 + k_{-1})$ (min.$^{-1}$).	10^4k_1 (min.$^{-1}$).	10^4k_{-1} (min.$^{-1}$).	Conversion at equilibrium (%).	K.
20·0°	0·138	22·9	21·3	1·6	92·9	13·1
20·0	0·690	22·5	21·5	1·0	95·5	21·2
20·0	1·38	22·7	21·9	0·8	96·5	27·6
20·0	2·76	20·6	20·0	0·6	96·9	31·3
50·0	0·138	303	255	48	84·0	5·25
50·0	0·690	305	272	33	89·0	8·1
50·0	1·38	297	271	26	91·1	10·2
50·0	2·76	269	250	19	93·1	13·5

It was found that the rate constants k and k_1 were independent of the initial acraldehyde concentration within the range 0·138—1·38M.; for 2·76M-acraldehyde solutions, however, the rate constants were lower by about 10% (Table II). This reduction is attributed to the changes in solvating and proton-donating properties of the reaction medium caused by the relatively high concentration of acraldehyde (~6 mol.-%), by analogy with the effect (cf. Braude *et al.*, *J.*, 1944, 443; 1948, 1982) of increasing concentrations of oxygenated organic substances in the reaction medium on the reaction rate and acidity function.

FIG. 1.

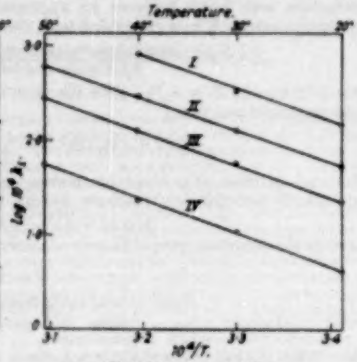
Arrhenius energy of activation.



Plot of "overall" k against 1/T.

FIG. 2.

Arrhenius energy of activation (hydration).



Plot of k_1 against 1/T.

Acid concns.: I, 3·8N.; II, 2·0N.; III, 1·0N.; IV, 0·2N.

The rate constants k increased with increasing acid concentration (Table I), but were not directly proportional to the stoicheiometric concentration of sulphuric acid, a relationship found by Pressman and Lucas (*loc. cit.*) to hold for 0·25N- and 0·5N-perchloric acid. Thus the ratio of k to c_A (Table I) increased greatly with acid concentration. The relation between k and acidity was accurately expressed for sulphuric acid concentrations between 0·20 and 2·00N. by Hammett and Deyrup's acidity function equation (*J. Amer. Chem. Soc.*, 1932, **54**, 2721), *viz.*, $H_0 + \log k =$ constant, where H_0 is the acidity function, a measure of the tendency of the medium to donate a proton to a neutral base. For 3·8N-sulphuric acid the value of $H_0 + \log k$ was somewhat low.

Measurements at different temperatures showed that the rate constants k, k_1, and k_{-1} accurately obeyed the Arrhenius equation, the linearity of the $\log k$–$1/T$ plots (Figs. 1, 2, and 3) being very marked.

The difference between the Arrhenius energies of activation (Tables III and IV) of the backward and the forward reaction (ΔE), *i.e.*, the heat of reaction, when 0·20—2·00N-sulphuric acid was used, was found to be 6·0 ± 0·2 kcals. per mol. This agreed closely with the value found by Pressman and Lucas (*loc. cit.*), *viz.*, 5·8 kcals. per mol., for ΔE under very different reaction conditions.

TABLE III.

Arrhenius energies of activation (in kcals./mol.).

Calculated from Table I. Initial acraldehyde concn. = 0·690M. throughout. Temp. range: 20·0—50·0°. $E = 2{\cdot}303 \times 1{\cdot}986 \times \frac{T_2T_1}{T_1 - T_2} \times \log (k_1/k_2)$.

H_2SO_4 concn. (N.).	$E_{(k_1+k_{-1})}$.	$E_{(k_1)}$.	$E_{(k_{-1})}$.	$\Delta E = [E_{(k_{-1})} - E_{(k_1)}]$.
0·20	16·5	16·1	22·2	6·1
1·00	16·3	15·8	21·9	6·1
2·00	15·6	15·1	21·0	5·9
3·80	15·7	15·4	20·8	5·4

TABLE IV.

Arrhenius energies of activation (in kcals./mol.).

Calculated from Table II; H_2SO_4 concn. = 1·00N. throughout.

Initial acraldehyde concn. (M.).	$E_{(k_1+k_{-1})}$.	$E_{(k_1)}$.	$E_{(k_{-1})}$.	ΔE.
0·138	16·2	15·5	21·3	5·8
0·690	16·3	15·9	21·9	6·0
1·38	16·1	15·6	21·6	6·0
2·76	16·1	15·8	21·7	5·9

TABLE V.

Effect of mercuric sulphate.

Temp. = 50·0°; H_2SO_4 concn. = 1·00N.; initial acraldehyde concn. = 0·690M. throughout.

$HgSO_4$ concn. (% w/v)	nil	1	5	10
$10^4(k_1 + k_{-1})$ (min.$^{-1}$)	305	358	394	407

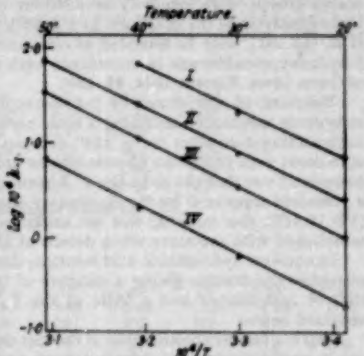
Addition of mercuric sulphate to the hydration mixture resulted in a considerable increase in the overall rate constant k (Table V); the rate of polymerisation of the aldehyde also appeared to be increased greatly, and solid deposits were observed in two runs before equilibrium had been attained.

Although the rate constants k and k_1 were independent of the initial acraldehyde concentration (see above) the rate constants k_{-1}, which were calculated by difference (Table II) and were much less accurate than the other rate constants, appeared to be appreciably affected by the initial acraldehyde concentration; in this connection it is noteworthy that the initial acraldehyde concentration also affected the equilibrium constants K, and these effects are probably related to the rapid reversible dimerisation of β-hydroxypropaldehyde which is discussed later.

The reversibility both of the dimerisation of the hydroxy-aldehyde and of the hydration of acraldehyde was proved in the course of kinetic experiments on the dehydration of the former. In view of its rapid dimerisation (see below) its dimer was used as the starting material for these experiments; in acid solution, under conditions exactly analogous to those under which the hydration had been studied, it was found that olefinic unsaturation appeared (*i.e.*, dehydration occurred) at an overall rate in satisfactory agreement with that of the hydration reaction; similar agreement was found for the equilibrium constants and for the energies of activation of the forward and the reverse reaction (cf. Experimental). The wide limits of error deemed "satisfactory agreement" are due to the inaccuracies inherent in the study of a reaction which reaches equilibrium at a conversion of less than 15%.

FIG. 3.

Arrhenius energy of activation (dehydration).



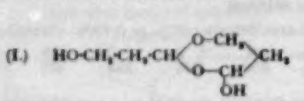
Plot of k_{-1} *against* 1/T.

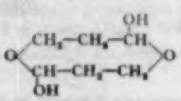
Acid concns.: I, 3·8N.; II, 2·0N.; III, 1·0N.; IV, 0·2N.

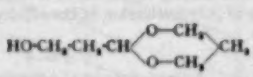
The isolation of pure β-hydroxypropaldehyde from the product of the acid-catalysed hydration had not previously been reported, and was thought by Helberger (PB 19,417) to be impracticable. In the present investigation it was found that after hydration at 50° for a time just sufficient to establish equilibrium and after careful neutralisation (pH 6—7) of the acid catalyst with solid calcium carbonate, 93% of acraldehyde had been converted and 96% of the initial aldehyde function remained in solution; the concentrate, obtained by passing the neutralised solution three times through a falling-film evaporator, contained about 10—20% water, and about 80—85% of the initial aldehyde function (by oxime determination). This concentrate was slowly distilled under oil-pump pressure at the lowest practicable bath temperature (cf. Glattfield and Sander, *J. Amer. Chem. Soc.*, 1921, **43**, 2675); in spite of these precautions, much resinification took place and the yield of pure β-hydroxypropaldehyde of b. p. 38°/0·2 mm. was low, amounting to a maximum of 20% of the theoretical weight.

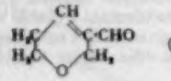
The distillate, a comparatively mobile oil, was observed to become warm spontaneously within a few minutes of distillation, giving a viscous oil of n_D^{20} 1·4783, presumably the so-called "β-hydroxypropionaldehyde lactol" of Bergmann, Miekeley, and Lippmann (*Ber.*, 1929, **62**, 1467). By analogy (cf. Späth and Schmid, *Ber.*, 1941, **74**, 859) with acetaldol (which in our hands dimerised more slowly than β-hydroxypropaldehyde) this substance is now assigned the formula of the hemiacetal (I), and not the symmetrical formula (II) proposed by Bergmann *et al.* (*loc. cit.*).

The unsymmetrical structure (I) was shown to be correct by acetylation of the dimer by the method of Bergmann *et al.* (*loc. cit.*), and by hydrolysis of the diacetate with 0·05N-aqueous hydrochloric acid at 70° (cf. Späth and Schmid, *loc. cit.*), whereby it was found that the two

(I.) 

(II.) 

(III.) 

(IV.) 

acetyl groups were removed at different rates (Table VI). This, in conjunction with the hydrogenolysis of the diacetate to 2-2′-hydroxyethyl-1 : 3-dioxan (III), reported by Bergmann *et al.* (*loc. cit.*), may be accepted as conclusive proof of the unsymmetrical structure of dimeric β-hydroxypropaldehyde in accordance with the predictions of Späth and Schmid (*loc. cit.*) and of Owen (*Ann. Reports*, 1944, **41**, 139).

Reaction of the dimer of β-hydroxypropaldehyde with 2 : 4-dinitrophenylhydrazine in anhydrous methanol containing a little concentrated sulphuric acid rather surprisingly gave a high-melting derivative (m. p. 228°, decomp.), the ultra-violet light absorption of which was in agreement with that of an αβ-unsaturated aldehyde (cf. Braude and Jones, *J.*, 1945, 498). This compound was thought to be the 2 : 4-*dinitrophenylhydrazone* of 3-formyl-Δ^3-dihydropyran (IV), a postulate supported by the elementary analysis. In view of the work reported by Helberger (PB 19,417), this material was not examined further but it is hoped that its identity may be established with certainty when details of Helberger's work become available.

In aqueous hydrochloric acid solution, dimeric β-hydroxypropaldehyde reacted with 2 : 4-dinitrophenylhydrazine giving a mixture of its own 2 : 4-*dinitrophenylhydrazone*, together with that of acraldehyde and a little of the 2 : 4-dinitrophenylhydrazone, m. p. 228° (decomp.), obtained before.

This is a further confirmation of the fact that dimeric and monomeric β-hydroxypropaldehyde are in equilibrium in the solutions used, as is the case with the homologue, acetaldol (Späth, Lorenz, and Freund, *Ber.*, 1942, **75**, 1029); a further equilibrium is set up in acid solution between β-hydroxypropaldehyde and acraldehyde. The formation of the 3-formyl-Δ^3-dihydropyran may thus be explained by assuming a union of the two aldehydes, or a self-condensation of the former, and subsequent loss of water.

Experimental.

Materials.—Acraldehyde was fractionated before use through a 2-ft. glass column packed with single-turn glass helices; it had b. p. 51—52° and was stabilised by the addition of 0·2% (w/v) of quinol. Analysis both by oximation and by bromine absorption showed 92% purity; the remaining 8% was water.

Pure acraldehyde (100·3% by oximation; 99·4% by bromine absorption) was used in some runs which, however, gave kinetic results in close agreement with those obtained with 92% acraldehyde.

Kinetic Measurements.—The kinetic runs were carried out in 100 ml. of reaction medium in two-necked Pyrex flasks; one neck carried a double-surface condenser connected to a vent line. Samples were withdrawn through the other neck by means of calibrated, narrow-stem, rapid-delivery 1-ml. or 2-ml. or of calibrated bulb 5- or 10-ml. pipettes connected to a suction line. The reaction vessels were kept in a water tank, thermostatically controlled to within ±0·05° by a mercury–toluene bulb thermoregulator. All runs were carried out in duplicate.

To start a run the solution of the acid was rapidly added to the acraldehyde solution, both solutions having been pre-heated to the required temperature. The flask was vigorously shaken and a sample was taken from the homogeneous medium; the whole operation took less than 12 seconds. Four or five further samples and two equilibrium samples were analysed in the course of each run by the bromine absorption method, and two or three samples per run by the oximation method for aldehyde content.

The bromine absorption method (see below) of analysis gave very consistent results and the rate constants of any one run were generally within ±3%. Three runs in which the variation of rate constants exceeded ±5% were rejected and repeated. Duplicate runs then agreed to within ±3%. Average values of the duplicate runs are recorded in Tables I and II. Three typical runs are given below, titres being in ml. of 0·1*N*-sodium thiosulphate:

(*a*) 2·00*N*-H_2SO_4; 0·690*M*-acraldehyde; 20·0°.

Time (mins.)	0	30	60	91	122	155	630	900
Bromine absorption titre of 1·00 ml.	13·75	11·78	10·13	8·46	7·28	6·14	0·55	0·55
10^4k (min.$^{-1}$)	—	53·9	53·3	56·2	55·1	55·4	—	—

Concn. of acraldehyde at equilibrium : 4·0% of initial concn. 10^4k (average) : 54·6 min.$^{-1}$.

(*b*) 2·00*N*-H_2SO_4; 0·690*M*-acraldehyde; 50·0°.

Time (mins.)	0	3	7	11	15	19	60	80
Bromine absorption titre of 1·00 ml.	12·46	10·49	8·48	6·70	5·46	4·40	1·35	1·37
10^4k (min.$^{-1}$)	—	648	637	668	662	680	—	—

Concn. of acraldehyde at equilibrium : 11·0% of initial concn. 10^4k (average) : 659 min.$^{-1}$.

(*c*) 1·00*N*-H_2SO_4; 0·138*M*-acraldehyde; 20·0°.

Time (mins.)	0	60	121	180	301	1200	1520
Bromine absorption titre of 5·00 ml.	13·78	12·10	10·66	9·35	7·22	1·00	0·99
10^4k (min.$^{-1}$)	—	23·4	23·0	23·5	23·8	—	—

Concn. of acraldehyde at equilibrium : 7·2% of initial concn. 10^4k (average) : 23·4 min.$^{-1}$.

The experimental conditions of the dehydration, carried out with dimeric β-hydroxypropaldehyde as starting material, were in every way analogous to those described above. In view of the low accuracy to be expected from these experiments, the following two runs only were performed (in duplicate), both with 1·00*N*-sulphuric acid and 0·065*M*-dimeric aldehyde (*i.e.*, 0·130*M*-β-hydroxypropaldehyde), titres being recorded as above:

(*a*) At 20·0°.

Time (mins.)	(i)	120	180	240	340	1440
Bromine absorption titre of 10·0 ml.		0·36	0·55	0·64	0·82	1·33
10^4k (min.$^{-1}$)		26·3	29·6	27·3	28·2	—
Time (mins.)	(ii)	125	180	240	334	1440
Bromine absorption titre of 10·0 ml.		0·37	0·54	0·66	0·79	1·33
10^4k (min.$^{-1}$)		26·1	28·9	28·5	27·1	—

Concn. of acraldehyde at equilibrium (% of initial aldehyde function) : 5·2.
10^4k (average) : (i) 27·9 min.$^{-1}$; (ii) 27·7 min.$^{-1}$.
$K = 19·2$; $k_1 = 26·4$ min.$^{-1}$; $k_{-1} = 1·4$ min.$^{-1}$.

(*b*) At 50·0°.

Time (mins.)	(i)	6	9	12	15	18	21	180
Bromine absorption titre of 10·0 ml.		0·47	0·75	0·93	1·09	1·29	1·38	3·19
10^4k (min.$^{-1}$)		265	298	287	276	288	270	—
Time (mins.)	(ii)	3	6	9	12	15	20	150
Bromine absorption titre of 10·0 ml.		0·24	0·45	0·71	0·91	1·13	1·28	3·19
10^4k (min.$^{-1}$)		261	253	279	280	291	256	—

Concn. of acraldehyde at equilibrium (% of initial aldehyde function) : 12·4.
10^4k (average) : (i) 281 min.$^{-1}$; (ii) 270 min.$^{-1}$.
$K = 7·0$; $k_1 = 241$ min.$^{-1}$; $k_{-1} = 34·4$ min.$^{-1}$.

Calculated Arrhenius energies of activation (in kcals./mol.):

$$E_{(k_1+k_{-1})}\ 14·4,\ E_{(k_1)}\ 13·9,\ E_{(k_{-1})}\ 20·1.\quad \Delta E = E_{(k_{-1})} - E_{(k_1)} = 6·2 \text{ kcals. per mol.}$$

Analytical Procedures.—(A) *Bromine absorption.* The sample was run into 20·0 ml. of standard (0·1*N*.) bromide–bromate reagent at 0°; after acidification with an excess of diluted (1 : 1) "AnalaR" hydrochloric acid, the mixture was kept at 0° for 30 seconds, treated with cold 20% w/v

aqueous potassium iodide solution, diluted with 100 ml. of distilled water, and titrated with standard 0·1*N*-thiosulphate solution without indicator. Blank determinations were performed on the bromide–bromate reagent to permit calculation of unsaturation. Under the above conditions β-hydroxypropaldehyde was *not* brominated.

(B) *Oximation.* The sample was run into 50 ml. of neutral hydroxylamine hydrochloride reagent (20 g. of hydroxylamine hydrochloride per litre of approx. 90% ethanol, containing 25 ml. of 0·2% w/v alcoholic bromophenol-blue). After being heated (under reflux) on the steam-bath for 20 minutes, the solution was titrated at room temperature with 0·1*N*-sodium hydroxide solution. Blank determinations, performed under conditions identical but for the absence of hydroxylamine hydrochloride from the reagent solution, gave corrections for the acidity of the hydration mixture. Cf. Maltby and Primavesi, *Analyst*, 1949, **74**, 498.

Preparation of β-Hydroxypropaldehyde.—A mixture of acraldehyde (75 ml.; purity 92%; 1 mol.), 3*N*-sulphuric acid (100 ml.), and water (325 ml.) was kept at 50° for 2·5 hours. The solution, the volume of which had decreased to 475 ml. (at room temp.), was rapidly cooled to 0°, and a sample was analysed; the acraldehyde conversion, determined by bromine absorption, was 93%, and the loss of aldehyde less than 1% (by oximation). Solid calcium carbonate was slowly added to the stirred solution until it was neutral (pH 6·8) to methyl-red (external indicator). After filtration under suction and thorough washing of the residue with distilled water, the solution (about 550—600 ml.) contained 96% of the initial amount of aldehyde function (by oximation).

The neutralised hydration medium was passed through a falling-film evaporator kept under vacuum (12 mm.); the evaporation surfaces were steam-heated, and the contact time was less than 20 seconds. The volume of liquid was reduced by about 40—50% per pass and generally three passes sufficed to remove about 85—95% of the water. The total loss of aldehyde function in these operations varied from 12 to 18%, 7%, presumably, being accounted for as unreacted acraldehyde.

The crude β-hydroxypropaldehyde (70—80 g.), containing about 15—25% of its weight of water and some polymeric material, was then distilled at the oil-pump under about 0·1—0·5 mm. The pure aldehyde (12—15 g.) distilled very slowly at 38—45°/0·2—0·5 mm. (Glattfield and Sander, *loc. cit.*, give b. p. 80—86°/14 mm.), and extensive reinification of the flask contents took place.

Dimeric β-Hydroxypropaldehyde (*4-Hydroxy-2-2′-hydroxyethyl-1 : 3-dioxan*).—The distillate from the above preparation became warm spontaneously and thickened to a viscous oil, n_D^{20} 1·4783, which was redistilled. Again, distillation proceeded slowly and some non-volatile, resinous material (2·5 g.) remained in the still. The distillate (10—12 g.), b. p. 40°/0·2 mm., n_D^{20} 1·4416, became warm spontaneously and gave the viscous dimer, n_D^{20} 1·4783 [Found: C, 49·05; H, 8·05; *M* (cryoscopic in dioxan), 152, 146. Calc. for $C_8H_{16}O_4$: C, 49·65; H, 8·15%; *M*, 148]. Oximation of the dimer by the procedure outlined above showed the presence of 1·99 potential carbonyl groups per mol., *i.e.*, the dimer behaved analytically as monomeric β-hydroxypropaldehyde.

2 : 4-*Dinitrophenylhydrazones.* (i) In anhydrous methanol. The dimeric aldehyde (1 g.) was dissolved in methanol (10 ml.) containing concentrated sulphuric acid (1 g.) and 2 : 4-dinitrophenylhydrazine (1·5 g.). After two days a solid (1·2 g.), probably *3-formyl-Δ²-dihydropyran* 2 : 4-*dinitrophenylhydrazone*, m. p. 214° (decomp.), had separated. After crystallisation from benzene containing 10% of ethyl acetate and chromatography on alumina (Peter Spence, type H) from benzene solution, it had m. p. 226° (decomp.) (Found: C, 49·35; H, 4·5. $C_{12}H_{12}O_5N_4$ requires C, 49·3; H, 4·15%), and light absorption maximum (in EtOH) at 3770 A., ε = 30,000.

(ii) In water. Dissolution of the dimeric aldehyde (1·5 g.) in a 2*N*-hydrochloric acid solution of 2 : 4-dinitrophenylhydrazine (2·5 g.) gave, within 5 minutes, a yellow precipitate (2 g.), m. p. 95—100°, which resolidified and then melted at 155—160° (decomp.). Chromatography of this material from benzene solution on alumina separated three substances: the most readily eluted was acraldehyde 2 : 4-dinitrophenylhydrazone (about 80 mg.), m. p. 161—162° (mixed m. p. with authentic material of m. p. 164° was 162—163°), light absorption maximum (in EtOH) at 3690 A., ε = 25,000 (Braude and Jones, *J.*, 1945, 498, give $\lambda_{max.}$ 3660 A., ε = 25,500). The intermediate benzene eluates contained slightly impure (?) 3-formyl-Δ²-dihydropyran 2 : 4-dinitrophenylhydrazone (about 150 mg.), m. p. 217—219° (decomp.), light absorption maximum (in EtOH) at 3770 A., ε = 31,000. The most strongly adsorbed material was eluted with benzene–ethyl acetate (5 : 1) and consisted of *β-hydroxypropaldehyde* 2 : 4-*dinitrophenylhydrazone* (about 1 g.), m. p. 110°. This was once more chromatographed and then recrystallised from benzene. It finally had m. p. 132·5—133° (Found: C, 42·85; H, 4·25; N, 21·6. $C_9H_{10}O_5N_4$ requires C, 42·55; H, 3·95; N, 22·05%) and light absorption maximum (in EtOH) at 3600 A., ε = 24,000.

Structure of Dimeric β-Hydroxypropaldehyde.—The dimeric aldehyde (5 g.) was acetylated by the method of Bergmann *et al.* (*Ber.*, 1929, **62**, 1467) by being kept with acetic anhydride (10 ml.) and pyridine (10 ml.) at room temperature for 24 hours. Ether (150 ml.) was then added and the solution was washed with *N*-aqueous sodium hydroxide, *N*-aqueous hydrochloric acid, and, finally, water. The ethereal layer was dried and evaporated at 12 mm., leaving an oil (2·8 g.) which was fractionated. The product (2·1 g.), 4-acetoxy-2-2′-acetoxyethyl-1 : 3-dioxan, had b. p. 96°/0·1 mm., n_D^{20} 1·4489 (Found: C, 51·65; H, 7·4. Calc. for $C_{12}H_{18}O_6$: C, 51·7; H, 6·95%). Bergmann *et al.* (*loc. cit.*) give b. p. 122—123°/0·5 mm., n_D^{20}

TABLE VI.

Hydrolysis of 4-acetoxy-2-2′-acetoxyethyl-1 : 3-dioxan by 0·05N-HCl at 70·0°.

Time (mins.).	Titre (ml. 0·01*N*-NaOH).	Diff. from blank (ml.).	Acetyl groups hydrolysed.	Time (mins.).	Titre (ml. 0·01*N*-NaOH).	Diff. from blank (ml.).	Acetyl groups hydrolysed.
Blank	24·20	—	—	70	28·40	4·2	1·7(5)
0	26·05	1·85	0·7(5)	90	28·70	4·5	1·9
5	26·70	2·5	1·0(5)	110	28·85	4·65	1·9(5)
10	26·90	2·7	1·1(5)	120	29·0	4·8	2·0
20	27·20	3·0	1·2(5)	130	29·1	4·9	2·0(5)

1·4490. This diacetate was hydrolysed by the method used by Späth and Schmid (*Ber.*, 1941, **74**, 899) for the hydrolysis of acetaldol dimer diacetate: it (0·1114 g.), n_D^{20} 1·4489, was added to approximately 0·05*N*-aqueous hydrochloric acid (100 ml.) at 70·0° ± 0·3°. Samples (5 ml.) of the homogeneous solution were titrated against freshly prepared 0·01*N*-sodium hydroxide solution (phenolphthalein indicator). Boiled-out distilled water was used for the hydrolysis and titration. Results are given in Table VI.

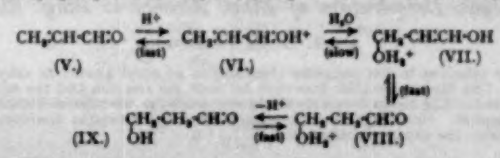
Discussion.

Previous discussions of the mechanism of hydration reactions based on kinetic work have dealt largely with the hydration of reactive olefins (Lucas *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 460, 2138; cf. Hammett, *op. cit.*, p. 292) and it has been postulated that an intermediate carbonium ion is formed by interaction of the olefin with a solvated hydrogen ion. Evidence adduced in favour of this mechanism included the fact that the rate of hydration is of the first order with respect to both the hydrocarbon and the catalyst concentration, the proportionality of the reaction rate to acid concentration in mixtures at constant ionic strength, and the similarity of the effects of different strong acids.

The hydration of αβ-unsaturated carbonyl compounds was investigated by Lucas *et al.* (*J. Amer. Chem. Soc.*, 1937, **59**, 1461; 1942, **64**, 1122, 1953; 1944, **66**, 1818), and interpreted in the case of mesityl oxide, of acraldehyde, and of 3-methylbut-2-en-1-al in terms of two simultaneous reactions, a hydroxonium-ion-catalysed hydration of "uncomplexed," and to a less extent of "complexed" starting material, *i.e.*, hydration *via* a carbonium ion and an oxonium ion, respectively. Evidence put forward for this dual mechanism is the observed increase in the ratio of rate constant to acid concentration with increasing acid concentration (from 0·2 to 2·0*N*.); Lucas *et al.* appear to interpret this as an increased contribution of the oxonium-ion mechanism at higher acidities, although it is probably better ascribed to effects of the medium as represented by Hammett's acidity function.

The salient experimental facts emerging from the present work are: the hydration is an equilibrium reaction (the equilibrium being approachable from both sides) of the first order with respect to acraldehyde, the rate constants being independent of initial acraldehyde concentration within the range studied. The dependence of the rate constants (between 20° and 50°) on the acid concentration is accurately expressed by Hammett's acidity function (data for the temperature dependence of which are not available in the literature). This is a criterion for specific hydrogen-ion catalysis, in view of the non-proportionality of rate constants to stoicheiometric acid concentration (cf. Hammett *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 830; 1936, **58**, 2182; 1939, **61**, 2791). The Arrhenius energies of activation of the hydration and dehydration reactions determined experimentally are 15·7 ± 0·4 and 21·6 ± 0·6 kcals. per mol., respectively, over the wide range of conditions examined: the rate-determining step of the dehydration is therefore unlikely to involve the normal ionic or covalent fission of a carbon–oxygen bond, as the energy requirements for these would be higher. Moreover, the comparatively small difference (6·0 ± 0·2 kcals. per mol.) in these energies of activation (which is equal to the heat of reaction) makes it appear probable that both the hydration and the dehydration proceed through the same rate-determining step.

The following mechanism is in accord with the facts observed and the deductions listed above. The first step of the hydration reaction is the reversible, fast (cf. Braude, *J.*, 1944, 447; Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686), acid-induced transfer of a hydrogen ion from its solvate to the carbonyl group of acraldehyde (V) to give the oxonium ion (VI); during the next



step, the rate-determining nucleophilic addition of a water molecule, the charge on the ion is redistributed, and the conjugate acid of an enol (VII) is produced which reverts to the carbonyl compound, the conjugate acid (VIII) of β-hydroxypropaldehyde; this tautomerisation would be expected to be fast (cf. Remick, "Electronic Interpretation of Organic Chemistry," J. Wiley and Sons, Inc., 1943, p. 376) and is therefore unlikely to constitute the rate-determining step. Fast reversible loss of a hydrogen ion from the conjugate acid finally affords β-hydroxypropaldehyde.

In the dehydration of this aldehyde the same steps are followed in the reverse order. The first is the fast acid-catalysed transfer of a hydrogen ion from the solvate to the aldehyde (IX); this will take place at the oxygen atom of the alcohol and not at that of the carbonyl group, as a carbonyl compound has stronger proton-donating (and thus weaker proton-accepting) properties than has an alcohol (cf. Braude *et al.*, *J.*, 1948, 1971, 1982). The oxonium ion (VIII) formed undergoes acid-catalysed enolisation (cf. Hammett, *op. cit.*, p. 231), generally a slow reaction (cf. Remick, *op. cit.*, p. 375) which in the case of the halogenation of carbonyl compounds constitutes the rate-determining step (Lapworth, *J.*, 1904, **85**, 30; Bell, "Acid-Base Catalysis," Oxford, Clarendon Press, 1941, pp. 82, 69, 137); the rate of enolisation of acetone thus determined is, however, still about ten times as great as that of the dehydration of β-hydroxypropaldehyde under consideration here. Moreover, in the present case the charge on the oxonium ion (VIII) may be expected to facilitate tautomerisation, and it is thus most unlikely that the enolisation step is rate-determining in the dehydration of β-hydroxypropaldehyde. This makes it seem more likely that the rate-determining step is the loss of water from the enol (VII) which proceeds with a simultaneous redistribution of the charge to give the oxonium ion (VI), which on loss of a hydrogen ion affords acraldehyde (V).

The essential rôle of the acid catalyst is thus to permit the formation of the oxonium ions (VI and VII), interconversion of which involves the addition or loss of a neutral water molecule. This step will require less energy than the addition of one ion to, or its separation from, another. The formation of the enolic ion (VII) from the conjugate acid (VIII) of β-hyroxypropaldehyde in the dehydration reaction is presumably necessary as the olefinic link of the enol (VII) provides a ready means of charge distribution during the loss of the water molecule, and thus of forming the conjugated system of the ion (VI).

Several effects observed in the present work are not readily predictable on the basis of the mechanism proposed, although they are not excluded by it. They include the variation of the equilibrium constant K with temperature, and the effect of acraldehyde concentration on the equilibrium constant and on the rate constant k_{-1} (cf. Table II). Whilst the former variation may be explained thermochemically, the latter effects are probably due to the dimerisation of β-hydroxypropaldehyde, which is, however, readily reversible and does not prevent an approach to the equilibrium from the β-hydroxypropaldehyde side.

No difficulty was experienced owing to the polymerisation or cyclic condensation of the aldehydes in solution, and the constancy of the equilibrium values (taken after 6 and 8 half-times of reaction) provides good evidence that these undesirable side reactions are very much slower than the hydration of acraldehyde under the conditions here examined.

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Research and Development Department,
The Distillers' Company Limited, Epsom, Surrey. [*Received, October* 13*th*, 1949.]

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97. *Equilibrium and Thermodynamic Relation in the Vapour-phase Catalytic Dehydration of Ethyl Alcohol to Ethyl Ether.*

By F. H. H. Valentin.

Equilibrium relations in the gas-phase dehydration of ethyl alcohol to ethyl ether have been studied. The thermo-dynamic functions for both the reaction and the substance ether have been derived. The values found for the heat content for ether are at variance with those previously accepted. Heat capacities calculated from spectroscopic functions agree with those derived from the experimental results.

In investigations on the formation of ether from alcohol it became necessary to find the requisite equilibrium and thermodynamic relations. For this we required suitable catalysts, a method of analysis for the reaction products, and a suitable apparatus for determination of the equilibrium constant.

Three groups of catalysts are known for the dehydration of alcohol to ether: aluminium oxide; aluminium sulphate; and sulphuric and phosphoric acids. A considerable number of alumina catalysts were investigated, but all were only slightly active at $<250°$, while at and

above that temperature they formed ethylene as well as ether and were thus unsuitable for equilibrium determinations. An alum catalyst prepared according to Jatkar and Watson (*J. Soc. Chem. Ind.*, 1926, **45**, 168T) was found to lead to ether exclusively and in good yield at 200—240°. For equilibrium determinations at lower temperatures a new catalyst was developed consisting of sulphuric acid, promoted with copper sulphate, on a silica-gel carrier. This catalysed the formation of ether from alcohol exclusively, at 120—170°.

The product of the dehydration reaction was analysed by a method based on the fluoroboric-acid-catalysed reaction with acetic anhydride (Valentin, *J. S. African Chem. Inst.*, 1949, **2**, 59).

Experimental.

Preparation of the Sulphuric Acid–Copper Sulphate Catalyst.—Commercial silica gel was washed in a stream of water for 12 hours, then dried, and heated at 350° for 4 hours in a slow current of air. The gel (125 g.) was then soaked for 2 hours in a solution of sulphuric acid (12 c.c.) and copper sulphate (4·5 g.) in water (388 c.c.). The solution was decanted and the gel dried in an oven at 105° for 8 hours. The soaking and drying were repeated 4 times, all the solution being then taken up by the gel. The final drying was for 16 hours.

Apparatus for Equilibrium Determinations.—This consisted of a jacketed 4-l. steel autoclave containing the catalyst spread on two porcelain basins one above the other. Electric heating of the bottom kept a liquid boiling under reflux in the jacket at an accurately controlled low pressure. This ensured precise temperature control by virtue of the high heat transfer coefficient from a condensing vapour to a metal surface. Tetralin, used up to 170°, and "Dowtherm," used at higher temperatures, satisfactorily maintain their vapour pressure–temperature relations. The lid of the autoclave was heated electrically. The whole apparatus was well lagged and the temperature was the same (within ½°) at the bottom, centre, and top.

Equilibrium constants.

Temp., °K.	392	403	413	425	431	437	463	473	482
K_p (this work)	0·23	0·40	0·57	0·87	1·05	1·22	—	2·51	3·10
K_p (lit.)	—	0·6 [1]	—	—	—	—	2·3 [2]	—	—
Temp., °K.	492	498	503	509	523	539	542	548	
K_p (this work)	3·51	—	3·66	3·88	—	—	—	—	
K_p (lit.)	—	3·5 [3]	—	—	6·9 [4]	7·75 [5]	8·3 [6]	1·0 [7]	

[1] Pease and Yung, *J. Amer. Chem. Soc.*, 1924, **66**, 2397. [2] Mailhe and de Godon, *Bull. Soc. chim.*, 1916, **5**, 565. [3] Jatkar and Watson, *J. Indian Inst. Sci.*, 1926, **9**, *A*, 71. [4] Clark, Graham, and Winter, *J. Amer. Chem. Soc.*, 1925, **47**, 2748. [5] Newitt and Semerano, *Proc. Roy. Soc.*, 1936, **157**, *A*, 348. [6] Alvarado, *J. Amer. Chem. Soc.*, 1928, **50**, 790.

Procedure for Equilibrium Measurements.—The autoclave containing 100 g. of catalyst was brought up to the required reaction temperature and evacuated. Alcohol (30 c.c.) were pumped in with a controlled-volume pump, conditions were kept constant until equilibrium was attained, and two samples (*ca.* 2 g. each) were withdrawn at an interval of 15 minutes and totally condensed. The water formed in the reaction was adsorbed more strongly than the alcohol, causing a slight fall in pressure inside the autoclave as the reaction proceeded. Completion of the reaction was indicated by the pressure becoming constant, and was confirmed by the concordant analyses of the two samples. The total time required for the reaction varied from 6 hours at the lowest temperature to 2 hours at the highest.

Results.—The pressure in the autoclave was kept at *ca.* 3 atm. and, since in the reaction there is no change in the number of molecules, K_p was taken as equal to K, within the limits of the experimental error. Results are given in the table.

The experimental results are represented by the empirical equation

$$\log K_p = 7{\cdot}70 - 2200T^{-1} - 1{\cdot}00 \log T \pm 0{\cdot}04$$

Thence other thermodynamic functions for the reaction were calculated, as follows:

$$\Delta F^\circ = 10{\cdot}061 + 4{\cdot}573T \log T - 35{\cdot}21T$$
$$\Delta H^\circ = 10{\cdot}061 - 1{\cdot}986T$$
$$\Delta C_p^\circ = -1{\cdot}986$$
$$\Delta S^\circ = 52{\cdot}8 - 4{\cdot}55 \log T - 10{\cdot}020T^{-1}$$

To minimise errors the following equation was used in calculating the entropy change

$$\Delta S^\circ = R\left(\frac{\mathrm{d} \log K_p}{\mathrm{d} \log T} + \log_e K_p\right)$$

Discussion.

Thermodynamic data for ether are calculated from those for the reaction, the best available data for alcohol and water being used. For alcohol

$$C_p^\circ = 3{\cdot}578 + 49{\cdot}847 \times 10^{-3}T - 169{\cdot}91 \times 10^{-7}T^2$$
$$H^\circ = -51{\cdot}762 + 3{\cdot}578T + 24{\cdot}924 \times 10^{-3}T^2 - 54{\cdot}64 \times 10^{-7}T^3$$
$$S^\circ = 31{\cdot}93 + 8{\cdot}239 \log T + 49{\cdot}85 \times 10^{-3}T - 84{\cdot}9 \times 10^{-7}T^2$$

[from Spencer and Flanagan (*J. Amer. Chem. Soc.*, 1942, **64**, 2511), Brickwedde, Moskow, and Aston (*J. Res. Nat. Bur. Stand.*, 1946, **37**, 263), and Aston (*Ind. Eng. Chem.*, 1942, **34**, 514)].

For water

$$C_p^\circ = 7{\cdot}219 + 2{\cdot}374 \times 10^{-3}T + 2{\cdot}67 \times 10^{-7}T^2$$
$$H^\circ = -57{\cdot}016 + 7{\cdot}219T + 1{\cdot}187 \times 10^{-3}T^2 + 0{\cdot}89 \times 10^{-7}T^3$$
$$S^\circ = 4{\cdot}06 + 16{\cdot}623 \log T + 2{\cdot}374 \times 10^{-3}T + 1{\cdot}34 \times 10^{-7}T^2$$

[from Spencer and Flanagan (*loc. cit.*), Brickwedde, Moskow, and Aston (*loc. cit.*), Giauque and Archibald (*J. Amer. Chem. Soc.*, 1937, **59**, 56), and Gordon (*J. Chem. Physics*, 1934, **2**, 65)].

Then for ether

$$C_p^\circ = 2{\cdot}049 + 97{\cdot}320 \times 10^{-3}T - 342{\cdot}49 \times 10^{-7}T^2$$
$$H^\circ = -36{\cdot}447 - 2{\cdot}043T + 48{\cdot}661 \times 10^{-3}T^2 - 112{\cdot}39 \times 10^{-7}T^3$$
$$S^\circ = 112{\cdot}58 - 4{\cdot}695 \log T + 97{\cdot}33 \times 10^{-3}T - 171{\cdot}1 \times 10^{-7}T^2 - 10{\cdot}0207T^{-1}$$
$$F^\circ = -36{\cdot}447 - 95{\cdot}057 - 48{\cdot}77 \times 10^{-3}T^2 + 56{\cdot}92 \times 10^{-7}T^3 + 4{\cdot}718T \log T.$$

These results are recorded in the following table, together with values in the literature, extrapolated values being marked with an asterisk.

Thermodynamic values for ethyl ether.

Temp., °K.	285	293	372	400	450	500
C_p° (this work)	—	—	29·4 [a]	31·4	34·6	37·9
C_p° (spec.) [a]	—	—	30·6	32·3	35·3	38·2
H°	—	−33,149 [b]	—	−30,196	−28,530	−26,714
S°	92·5 [b]	—	—	111·6	119·2	124·3

[a] Calc. from spectroscopic functions by Dobratz's method (*Ind. Eng. Chem.*, 1941, **33**, 759).
[b] Parks and Huffman (*J. Amer. Chem. Soc.*, 1924, **46**, 1753) give 88·9.
[b] The heat of combustion recorded by Stohmann, Rodatz, and Herzberg (*J. pr. Chem.*, 1887, **35**, 410) leads to H° −44,935.
[b] Jennings and Bixler (*J. Physical Chem.*, 1934, **38**, 747) give 32·1.

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Department of Chemistry and Chemical Technology,
University of Natal, Durban, South Africa. [*Received, September 26th*, 1949.]

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98. *Optical Activation by Asymmetric Solvent Action.*

By C. Buchanan and S. H. Graham.

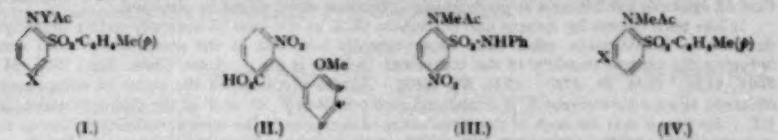
Both first- and second-order asymmetric transformations have been observed to occur when potentially optically active, but optically unstable, compounds are dissolved in an optically active solvent. The compounds so obtained have a sufficiently high rotation to allow observations to be made of their rates of racemisation in an inactive solvent and to compare the effect of substituents on the optical stability of closely related compounds.

The existence of a differential solvent effect of an optically active solvent on the two enantiomorphic forms of another active substance was established by Patterson and Buchanan (*J.*, 1940, 290: cf. also Patterson and Lamberton, *J.*, 1937, 1453) who showed that, while the molecular solution volumes of a pair of enantiomorphs were identical when measured in a symmetrical solvent, they differed by a small, but definite, amount when measured in an asymmetric solvent. Several workers have examined the possibility of resolving racemates by means of an asymmetric solvent, *e.g.*, by determining the solubility of the two enantiomorphs separately in an active solvent or by crystallising or extracting the racemate by means of an active solvent. No differentiation of the kind sought was found (Turner and Harris, *Quart. Reviews*, 1948, 327). Turner and Harris (*loc. cit.*) state that "Generally speaking, racemates cannot be even partially resolved by crystallisation from an optically active solvent. This is what might be expected, unless one antipode crystallised with solvent of crystallisation. An example remains to be discovered in which association with an optically active solvent, by hydrogen bonding for example, is responsible for solubility differences in a pair of optical isomerides . . . Some such loose association, with preference for one isomeride, must be responsible for cases of partial resolution by adsorption on optically active adsorbents." The very slight solvent effect observed by Patterson and Buchanan also supports the view that resolution of an optically stable compound is unlikely. We thought, however, that this effect might be made more manifest by examining optically unstable compounds of the type used in asymmetric trans-

formations, *i.e.*, that the asymmetric solvent might influence the relative stabilities and solubilities of these compounds in such a manner as to lead to products showing a measurable rotation. To test this possibility a representative series of optically active but optically unstable compounds was examined in an optically stable solvent.

The asymmetric solvent employed most generally was ethyl (+)-tartrate, which, apart from its ready availability, possessed several advantages. It is a most powerful solvent, a large variety of compounds of most diverse type dissolving in it, including the sodium salts of sulphonic acids. Owing to the fact that it is water-soluble its removal from solid materials after recrystallisation is a matter of extreme ease, while water-soluble compounds can be freed from it by extraction with ether.

The first compound to be examined extensively was 2-acetomethylamido-5 : 4'-dimethyldiphenyl sulphone (I, X = Y = Me), which owes its asymmetry to restricted rotation about



(I.) (II.) (III.) (IV.)

the bond joining nitrogen to the benzene ring. Experiments with this compound are typical of the procedure employed. A supersaturated solution, prepared by warming (I) with ethyl (+)-tartrate, was kept at room temperature till crystallisation appeared to be complete. The resulting crystals were separated as far as possible from the mother-liquor by filtration at the pump, washed with a little alcohol and copiously with water, and dried *in vacuo*. In chloroform solution these crystals gave a dextrorotation ($\alpha \sim +0{\cdot}2°$). The material remaining in the ethyl (+)-tartrate mother-liquors was precipitated by addition of water, washed, and dried: this gave a lævorotation ($\alpha \sim -0{\cdot}15°$) in chloroform solution. Both samples mutarotated to zero rotation, the half-life period at room temperature being 19 minutes.

When a sufficiently dilute solution of the sulphone in ethyl (+)-tartrate was kept at room temperature for a few hours so that no crystallisation occurred, the material in solution was found to be lævorotatory. As this was the whole amount of the originally optically inactive sulphone, a first-order transformation must have occurred, while the activity of the sample obtained by crystallisation was almost certainly due to a second-order transformation. It is of interest that this compound obeys the van't Hoff–Dimroth relationship, which states that the less soluble form of the compound should also be the less stable.

The same sample can be repeatedly activated in this manner and allowed to racemise in chloroform solution, each activation giving substantially the same rotation value, while the sample at the end remains unchanged in melting point. Thus the observed rotations cannot be due to any interaction between the solute and solvent with formation of an optically active impurity derived from the optically active solvent. Moreover, in several of the examples described below the observed rate of racemisation agrees well with that recorded by other workers who activated the substances by formation of diastereoisomeric salts in the normal manner.

With increase in temperature of the solution the activation effect decreases, and, in the case of this sulphone, is negligible at 84°. This temperature effect was observed to apply both to first- and to second-order transformations.

Compound (I) was also examined in other optically active solvents. Ethyl (−)-tartrate, as expected, gave the same results as ethyl (+)-tartrate except for the reversal of the direction of rotation, *i.e.*, the crystals were lævorotatory and the material precipitated from the mother-liquors dextrorotatory. (−)-Menthyl acetate gave a second-order transformation. No transformation was observed, however, when (+)- or (−)-*sec.*-octyl alcohol was used as asymmetric solvent. The solubility of the sulphone in cold *sec.*-octyl alcohol is low and crystallisation took place rapidly; crystallisation of the sulphone from ethyl tartrate took several days. However, crystallisation of the sulphone from menthyl acetate was also rapid, so it is difficult to say whether rate of crystallisation is an important factor.

The related *N*-ethyl compound (I; X = Me, Y = Et) has also been found to undergo both first- and second-order transformations in ethyl (+)-tartrate. As expected, it was found to be optically much more stable than the *N*-methyl compound, having a half-life period of about 6 hours as against 19 minutes. This is of interest as showing that a compound of such relatively

high optical stability is capable of undergoing asymmetric transformations in an asymmetric solvent.

Another closely related compound, sodium *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonate, was found to undergo a first-order transformation in ethyl (+)-tartrate and a second-order transformation in (+)-*sec.*-butyl alcohol. The half-life period of racemisation was 150 minutes at 18°; Mills and Kelham (*J.*, 1937, 274) give 175 minutes at 16·6° and 70 minutes at 25°.

These results show that optical activation can be achieved by asymmetric solvent action. Moreover, this method can be applied to compounds which lack a salt-forming group and so cannot be resolved by the normal means. The compounds obtained, although not optically pure, have a sufficiently high rotatory power to allow observations to be made of their rates of racemisation and thus to compare the optical stabilities of related compounds. It was decided to study a series of related sulphones and similar compounds in this way, in the hope that an example exhibiting a more complete activation effect might be obtained.

It has been shown by Adams and his school that, in the case of optically active diphenyl derivatives, substituents other than those actually involved in the steric interference can influence the optical stability of the compound (Adams *et al.*, *J. Amer. Chem. Soc.*, 1932, **54**, 2906, 4434; 1934, **56**, 1787; 1935, **57**, 1592). Adams investigated the series of compounds obtained when a substituent X is introduced into positions 3′, 4′, or 5′ of the diphenyl molecule (II). He found that for each of the three series of compounds the optical stability increases in the order $H < OCH_3 < CH_3 < Cl < Br < NO_2$. A similar investigation was carried out on the sulphone type of molecule. The substituents Cl, Br, OCH_3 were successively introduced in place of the *p*-methyl group (I; X = Cl, Br, OCH_3; Y = Me or Et); the *N*-methyl-*p*-bromo-compound, however, was not prepared in sufficient quantity for experiments with ethyl (+)-tartrate. Of these compounds, all underwent first-order transformations in ethyl (+)-tartrate and, with the single exception of the *N*-ethyl-*p*-chloro-compound, all underwent second-order transformations also. The relative optical stabilities are shown in Table I. Since the observed rotations are small, these values are only approximate, but they allow the various compounds to be arranged in order of optical stability, which decreases in the order $OCH_3 > CH_3 > Cl > Br$. It will be observed that the substituents fall into the same sequence as that observed by Adams but that the order is reversed.

TABLE I.

Half-life periods of racemisation of sulphones (I).

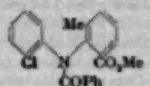
X =	Y = CH_3.	Y = C_2H_5.	X =	Y = CH_3.	Y = C_2H_5.
p-Br	—	30 mins.	*p*-CH_3	19 mins.	720 mins.
p-Cl	3 mins.	120 mins.	*p*-OCH_3	41 mins.	many hours

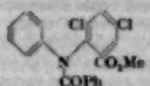
It was desired also to investigate the nitro-substituted sulphone (I; X = NO_2), but no route leading conveniently to its synthesis could be found. The closely related sulphonanilide (III) was not activated by ethyl (+)-tartrate, nor did 5-nitro-2-acetomethylamidobenzenesulphonic acid give any evidence of asymmetric transformation with brucine or quinidine. In so far as conclusions may be drawn from such negative results, it seems that a nitro-group *para* to the methylamido-group destroys the asymmetry of the molecule, possibly because of resonance involving both the nitro- and the amido-group.

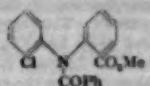
The unsubstituted and *m*-substituted compounds (IV; X = H, Br, Cl, CH_3, OCH_3) could not be activated by solution in ethyl (+)-tartrate. These observations were most surprising, having regard to the very consistent results obtained with the *p*-substituted sulphones. The explanation possibly lies in the difference in physical properties. The unsubstituted and *m*-substituted sulphones are much more soluble in common solvents than the *p*-compounds and display a greater tendency to form supersaturated solutions, the most extreme case being that of the *m*-chloro-compound, solutions of which in acetic acid remained supersaturated for up to two days, crystallising rapidly on the addition of a crystal of the sulphone. With one exception they did not crystallise from ethyl (+)-tartrate and had to be precipitated by water, the solute separating first as an oil which solidified on more or less prolonged standing. The *m*-nitro-compound (IV; X = NO_2), which did not display this tendency to form supersaturated solutions, was crystallised from ethyl (+)-tartrate but it gave no evidence of activation.

Derivatives of Benzodiphenylamide.—Three *o*-substituted benzodiphenylamides (V, VI, VII), compounds of low optical stability similar to compounds investigated by Turner and his school, have been examined. The acids corresponding to the first two of these esters have been resolved by Jamison and Turner (*J.*, 1940, 264), who measured their rates of racemisation;

both esters were observed to undergo both first- and second-order transformations in ethyl (+)-tartrate. The rotation of the product of the first-order transformation of (V) was the


(V.)


(VI.)


(VII.)

largest observed in the course of this work ($[\alpha]_{5461} = -4{\cdot}4°$). In this case the enantiomorph which is present in excess in solution also predominates in the crystals which separate out, which have $[\alpha]_{5461} = -0{\cdot}75°$. Crystallisation from ethyl (−)-tartrate gave a product having $[\alpha]_{5461} = +0{\cdot}79°$. The observed rates of racemisation (Table II) of these esters corresponded fairly satisfactorily with those recorded by Turner for the acids.

TABLE II.

	Half-life period, mins.		Half-life period, mins.
Acid (V)	10·5	Ester (V)	8
Acid (VI)	4·6	Ester (VI)	5

The third ester (VII) was observed to undergo a first- but not a second-order transformation. The crystals which separated from ethyl (+)-tartrate were optically inactive, but the material precipitated from the mother-liquors was lævorotatory. It is difficult to say why this compound should not have undergone a second-order transformation. It had been observed that, in the case of 2-acetomethylamido-5 : 4′-dimethyldiphenyl sulphone, any vigorous agitation of the ethyl (+)-tartrate solution while filtering the crystals, or any scratching or the walls of the containing vessel, caused precipitation of lævorotatory material from the mother-liquors along with the dextrorotatory crystals, thus obscuring the rotation of the material actually produced by crystallisation. It is possible that in this case also some form of coprecipitation obscures the effect of a possible second-order transformation. The half-life period of this compound was large compared with that of (VI) (15 mins. as against 5 mins.). This is not very surprising having regard to the observations made on the effect of substituents on the optical stability of the sulphones, and to similar observations in the diphenyl series recorded by Kuhn and Albrecht (*Annalen*, 1927, **458**, 221).

Prototropic Compounds.—A compound which exists in solution as an equilibrium mixture of two tautomers, one of which is asymmetric and the other symmetric, should be capable of undergoing asymmetric transformations. Only a few instances of this are recorded in the literature, and most of the compounds in question were unsuitable for the purposes of the present work. Leuchs and Wutke (*Ber.*, 1913, **46**, 2420; 1921, **54**, 1830) investigated two compounds of this type, 2-*o*-carboxybenzylindan-1-one and hydrocarbostyril-3-carboxylic acid. Of these, the first is difficult to prepare and the second sparingly soluble, so that only dilute solutions of the compound would be available for polarimetric examination and the slight activation to be expected by the use of an asymmetric solvent might be overlooked. More recently, Davidson and Turner (*J.*, 1945, 843) have shown that compounds of the malonoanilic acid type undergo asymmetric transformations with optically active bases.

One of these compounds, benzylmalono-*o*-toluidic acid, was prepared and recrystallised from ethyl (+)-tartrate. The material which crystallised was lævorotatory; no mutarotation occurred in alcoholic solution but the rotation disappeared on addition of alcoholic alkali. These observations are in accord with Turner's findings. No polarimetric measurements could be made on the material recovered from the ethyl tartrate mother-liquors owing to the presence of highly coloured impurities.

On the basis of Leuchs and Wutke's observations on the substituted indanone it seemed possible that the hydrogen atom attached to a carbon atom adjacent to a single carbonyl group might be sufficiently mobile to permit of asymmetric transformations. An α-alkyldeoxybenzoin was thought to be a suitable compound for experiment, and the α-benzyl compound was accordingly prepared. α-Benzyldeoxybenzoin, however, apparently reacted with ethyl (+)-tartrate to give a highly active product, which we were unable to isolate in a pure state and did not examine further. The related compound, *α-benzyldeoxybenzoin-2-carboxylic acid*, was resolved in the usual manner. This acid formed a brucine salt from which, after four crystallisations from ethyl acetate, the (−)-base, (+)-acid was isolated, $[\alpha]_{5461} = -12{\cdot}1°$. On treatment with hydrochloric acid, the (+)-acid was produced, $[\alpha]_{5461} = +27{\cdot}5°$. This

acid did not racemise in chloroform solution, as did that of Leuchs and Wutke. It racemised slowly, however, on crystallising from hot acetic acid; it also racemised in hot aqueous-alcoholic alkali. Esterification of the active acid with diazomethane produced the (+)-*methyl* ester, $[\alpha]_{5461} = +29{\cdot}3°$. This ester was heated under reflux in methanolic solution for 48 hours; the recovered ester had $[\alpha]_{5461} = +31{\cdot}8°$, showing that no racemisation had taken place in the process. The increase in rotation of the ester was presumed to be due to some purification that had taken place in the course of the attempted racemisation. This result is rather difficult to reconcile with Leuchs and Wutke's claims, but it indicates that α-benzyldeoxybenzoin itself would be unlikely to undergo an asymmetric transformation.

Optically inactive methyl α-benzyldeoxybenzoin-2-carboxylate was crystallised from ethyl (+)-tartrate solution. Almost all the ester separated from the solution: the crystals showed no rotation.

αα'-Dinitrodibenzyl, which contains the nitro-*aci*nitro-system, was also investigated. This substance has been shown to exist in two isomeric forms, one m. p. 235° and the other m. p. 152° (Schmidt, *Ber.*, 1901, **34**, 3540; Brown and Shriner, *J. Org. Chem.*, 1937—1938, **2**, 376). The compound contains two asymmetric carbon atoms; one of the isomers will be the racemic and the other the *meso*-form of the compound. No means of distinguishing them exists, since, as they lack any salt-forming group, no method of resolution, other than asymmetric solvent action, is applicable. It was hoped that the racemic form might undergo an asymmetric transformation in ethyl (+)-tartrate solution, and there was a possibility that the *meso*-form might undergo partial conversion into its isomer under the influence of the ethyl (+)-tartrate.

The higher-melting isomer crystallised rapidly from the ethyl tartrate. In the first experiment the crystals were found to be lævorotatory in nitrobenzene solution; mutarotation occurred at room temperature. A certain amount of decomposition of the dinitrodibenzyl had taken place, however, as indicated by the evolution of nitrous fumes; it had been necessary to heat the dinitrodibenzyl and the ethyl tartrate for rather a long time near the boiling point of the ethyl tartrate to bring the sparingly soluble nitro-compound into solution. The experiment was repeated, care being taken to avoid any decomposition of the nitro-compound; the crystals which separated were optically inactive. No rotation was detected in the crystals when the first crystals were allowed to separate at 86° (to permit of slow crystallisation). The rotation observed in the first instance was possibly due to chance preferential inoculation of the solution or to an asymetric decomposition. All these samples melted at 235°; there was no indication of any conversion into the lower-melting isomer. When the other isomer was crystallised from ethyl (+)-tartrate there was no indication of any asymmetric transformation or of any conversion into the higher-melting isomer.

Experimental.

(All polarimeter readings were made in a 2-dm. tube with mercury green light, λ = 5461 A.; all m. p.s are uncorrected.)

5-Substituted 2-Acetoalkylamido-4'-methyldiphenyl Sulphones.—The toluene-*p*-sulphonyl derivatives of *p*-methyl-, *p*-methoxy-, *p*-chloro-, and *p*-bromo-*N*-methyl- and *N*-ethyl-aniline were all prepared by normal methods. Rearrangement to the *o*-amino-sulphone was carried out by heating it at 100° with an equal weight of 96% sulphuric acid for 2 hours; when the mixture was cooled and poured into water the sulphones were precipitated. The following 2-amino-4'-methyldiphenyl sulphones were obtained: *N*-acetyl-*N*:5-dimethyl-, prisms, m. p. 168° (lit., 138°; Halberkaan, *Ber.*, 1921, **54**, 1835) (Found: C, 64·5; H, 5·8. Calc. for $C_{17}H_{19}O_3NS$: C, 64·4; H, 6·0%); *N*-acetyl-5-methyl-*N*-ethyl-, needles (alcohol), m. p. 145°; *N*-acetyl-5-methoxy-*N*-methyl-, prisms (alcohol), m. p. 138°; *5-methoxy-N-ethyl-*, prisms (alcohol), m. p. 94° (Found: C, 63·1; H, 6·3; N, 4·8. $C_{18}H_{21}O_3NS$ requires C, 63·0; H, 6·2; N, 4·6%); *N-acetyl-5-methoxy-N-ethyl-*, prisms (alcohol), m. p. 145° (Found: C, 62·6; H, 6·1; N, 4·3. $C_{19}H_{23}O_3NS$ requires C, 62·2; H, 6·0; N, 4·0%); *5-chloro-N-methyl-*, needles (alcohol), m. p. 155° (Found: C, 57·1; H, 4·8; N, 5·1. $C_{16}H_{16}O_3NClS$ requires C, 56·9; H, 4·7; N, 4·7%); *5-chloro-N-acetyl-N-methyl-*, needles (alcohol), m. p. 159° (Found: C, 57·0; H, 4·7; N, 4·4. $C_{18}H_{18}O_4NClS$ requires C, 56·9; H, 4·7; N, 4·2%); *5-chloro-N-ethyl-*, needles (alcohol), m. p. 136° (Found: C, 58·1; H, 5·1; N, 4·8. $C_{17}H_{18}O_3NClS$ requires C, 58·2; H, 5·2; N, 4·5%); *5-chloro-N-acetyl-N-ethyl-*, plates (alcohol), m. p. 153° (Found: C, 58·0; H, 5·4; N, 3·7. $C_{19}H_{20}O_4NClS$ requires C, 58·0; H, 5·2; N, 4·0%); *5-bromo-N-methyl-*, needles (alcohol), m. p. 161° (Found: C, 50·0; H, 4·3. $C_{16}H_{16}O_3NBrS$ requires C, 49·7; H, 4·2%); *5-bromo-N-acetyl-N-methyl-*, needles (alcohol), m. p. 173° (Found: C, 50·1; H, 4·3. $C_{18}H_{18}O_4NBrS$ requires C, 50·3; H, 4·2%); *5-bromo-N-ethyl-*, needles (alcohol), m. p. 141° (Found: C, 50·9; H, 4·8. $C_{17}H_{18}O_3NBrS$ requires C, 50·9; H, 4·6%); *5-bromo-N-acetyl-N-ethyl-*, needles (alcohol), m. p. 144° (Found: C, 51·8; H, 4·6. $C_{19}H_{20}O_4NBrS$ requires C, 51·6; H, 4·6%).

2-Acetomethylamido-5:4'-dimethyldiphenyl Sulphone in Ethyl (+)-Tartrate.—(*a*) The sulphone (3 g.) was dissolved in ethyl (+)-tartrate (10 c.c.). After 5 hours at room temperature the sulphone was precipitated by addition of water, filtered off, washed thoroughly with water, and dried *in vacuo*; 1·336 g. in chloroform (15 c.c.) had α^{18} −0·20°, rising to zero, half-life period = 19 minutes.

(*b*) The sulphone (5 g.) was crystallised from ethyl (+)-tartrate (7 c.c.). When crystallisation

appeared to be complete, the crystals were carefully drained as free from ethyl tartrate as possible, washed with a little alcohol, then washed thoroughly with water, and dried *in vacuo*. It was essential not to scratch or in any way agitate the crystals while they were still in contact with ethyl tartrate, as this caused precipitation of lævorotatory material from the mother-liquors. The material remaining in the mother-liquors was precipitated and treated as in (*a*) above. Crystals: 2·034 g. in 15 c.c. of chloroform had α^{17} +0·17°, falling to zero, half-life period = 19 minutes. Precipitate: 1·271 g. in 15 c.c. of chloroform had α^{16} −0·15°, half-life period of mutarotation = 19 minutes.

Effect of increase of temperature. The sulphone (5 g.) was crystallised from ethyl (+)-tartrate (7 c.c.) at 84°, and samples were kept in the ester solution at 42° and 84° for several hours without crystallisation taking place; the several fractions were then recovered in the appropriate manner. The samples treated at 84° possessed negligible rotations (*ca.* ±0·01° for 10% solutions in chloroform). The 42° sample had $[\alpha]_D^{17}$ −0·5° (*c*, 12 in chloroform).

2-Acetomethylamido-5:*4′-dimethyldiphenyl Sulphone in Other Asymmetric Solvents.*—(a) *Ethyl (−)-tartrate.* The sulphone (3 g.) was recrystallised from ethyl (−)-tartrate (5 c.c.). Crystals: 0·438 g. in 15 c.c. of chloroform had α^{20} −0·05°, rising to zero in 1 hour. Precipitate: 1·0446 g. in 15 c.c. of chloroform had α^{19} +0·13° falling to zero in 2 hours.

(b) (−)-*Menthyl acetate.* A solution of 3 g. in 20 c.c. was allowed to crystallise completely; the crystals were filtered off and washed with cold methanol: 1·03 g. in 15 c.c. of chloroform had α^{20} +0·05°, falling to −0·10° in 90 minutes, the final lævorotation being presumably due to the presence of residual menthyl acetate.

(c) (+)- *and* (−)-sec.-*Octyl alcohol.* Solutions of 3 g. of the sulphone in 10 c.c. each of the alcohols were allowed to crystallise; the crystals, representing almost the whole of the solute, were in both cases optically inactive.

2-Acetoethylamido-5:*4′-dimethyldiphenyl Sulphone in Ethyl (+)-Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). Crystals: 1·8184 g. in 15 c.c. of chloroform had α^{20} +0·11°, falling to zero, half-life period *ca.* 6 hours. Precipitate: 1·254 g. in 15 c.c. of chloroform had α^{20} −0·08°, rising to zero.

A solution of 1 g. in 10 c.c. of ethyl (+)-tartrate was kept for a few days, and the solute recovered by precipitation with water; 1·5177 g. in 15 c.c. of chloroform had α^{20} −0·08°, rising to zero.

Other Compounds of Type (I) *in Ethyl (+)-Tartrate.*—The compounds were in turn crystallised from ethyl (+)-tartrate (3 g. in 5—10 c.c.), giving two fractions, crystals, A, and precipitate from the mother-liquors, B. Samples (1 g.) of the sulphones were also kept in solution in ethyl (+)-tartrate (10 c.c.) for some hours and then the solute was recovered by precipitation with water to give fraction C. The observed rotations for the various fractions in chloroform solution (15 c.c.) of all these compounds are tabulated below.

Sodium N-Acetyl-N-methyl-p-toluidine-3-sulphonate in Asymmetric Solvents.—*N*-Methyl-*p*-toluidine was prepared by the method of Halberkaan (*loc. cit.*), and its acetyl derivative sulphonated and acetylated by the method of Mills and Kelham (*loc. cit.*). The hydrated salt melted at 84°.

(a) *Ethyl (+)-tartrate.* A solution of the salt (2 g.) in ethyl tartrate (5 c.c.) was kept at room temperature for 5 hours, and the solute recovered by precipitation with moist ether (use of dry ether led to difficulty in obtaining a solid precipitate). The salt was freed from ethyl tartrate by extraction with ether in a Soxhlet apparatus: 1·267 g. in 15 c.c. of water had α^{15} −0·08°, rising to zero, half-life period 150 minutes.

(b) (+)-sec.-*Butyl alcohol.* The salt (2 g.) was recrystallised from moist (+)-sec.-butyl alcohol (7·5 c.c.). The crystals were filtered off at the pump and washed with ether several times: 1·562 g. in 15 c.c. of water had α^{18} −0·07°, rising to zero in about 5 hours.

5-Nitro-2-methylaminobenzenesulphonanilide.—2-Chloro-5-nitrobenzenesulphonanilide was boiled for 48 hours in methanolic solution with an excess of methylamine carbonate; the *methylamine*-compound formed needles, m. p. 169°, from alcohol (Found: C, 51·0; H, 4·4; N, 13·8. $C_{13}H_{13}O_4N_3S$ requires C, 50·7; H, 4·2; N, 13·7%); its *acetyl* derivative (III) formed prisms, m. p. 222°, from dioxan (Found: C, 51·8; H, 4·4; N, 12·2. $C_{15}H_{15}O_5N_3S$ requires C, 51·6; H, 4·4; N, 12·0%). Crystallisation from ethyl (+)-tartrate gave an inactive product (*c*, 10 in dioxan).

Substituents.		A. Initial α.	A. Wt., g.	B. Initial α.	B. Wt., g.	C. Initial α.	C. Wt., g.	Half-life period.
X = OMe	Y = Me ...	−0·10°	0·432	−0·11°	0·962	−0·08°	0·746	41 mins.
	Y = Et ...	+0·03	0·494	−0·10	1·065	—	—	very large
X = Cl	Y = Me ...	−0·20	1·078	−0·10	0·975	−0·04	0·955	3 mins.
	Y = Et ...	nil	0·958	+0·14	0·756	+0·16	0·937	120 mins.
X = Br	Y = Et ...	−0·13	0·720	+0·12	0·750	—	—	30 mins.

Sodium 5-Nitro-2-methylaminobenzenesulphonate.—Dry *p*-nitro-*N*-acetyl-*N*-methylaniline (21·6 g.) was sulphonated with chlorosulphonic acid (13 g.) at 120—125° for 4 hours with stirring. The product was dissolved in water, neutralised with sodium carbonate, and evaporated to dryness. Crystallisation from 90% aqueous alcohol gave the hydrated *salt* as yellow needles (Found: C, 30·0; H, 3·8. $C_9H_7O_5N_2SNa,1·5H_2O$ requires C, 29·9; H, 3·6%). Acetylation gave the *N-acetyl* derivative, the hydrated salt being dehydrated at 100° (Found: C, 36·3; H, 3·2; N, 9·5. $C_9H_9O_6N_2SNa$ requires C, 36·5; H, 3·0; N, 9·5%).

(−)-*Brucine 5-Nitro-2-acetomethylamidobenzenesulphonate.*—The sodium salt (1·5 g.) in water (4 c.c.) was treated with a solution of brucine (2·3 g.) in water (10 c.c.) containing acetic acid (0·41 g.). The solution became deep red and on storage the *brucine* salt separated (Found: C, 57·4; H, 5·5; N, 8·4. $C_{32}H_{37}O_{10}N_4S$ requires C, 57·5; H, 5·1; N, 8·4%). The salt was recrystallised from water, alcohol, in which it was sparingly soluble, and nitrobenzene (readily soluble). The rotation in each case was

0·6° (*c*, 10 in chloroform). No change in rotation occurred on further recrystallisation from water; no mutarotation was observed. A saturated solution of the brucine salt in chloroform was treated with the theoretical quantity of alcoholic sodium ethoxide at 0°. The precipitated sodium salt was optically inactive. The zero value for the rotation of the brucine salt may be due to optical activation of the acid so that its rotation exactly counterbalances that of the brucine; but, in the absence of mutarotation or optical activity in the recovered acid, no definite conclusion can be drawn from anomalous rotation (*cf.* Kharasch *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 1646).

(+)-*Quinidine 5-Nitro-2-acetomethylamidobenzenesulphonate*.—The sodium salt (9·88 g.) in water (35 c.c.) was treated with quinidine (9·72 g.) in water (25 c.c.) containing acetic acid (1·6 g.). The precipitated yellow viscous oil slowly crystallised to pale yellow prisms of the quinidine salt (10 g.). The rotation ($[\alpha]_D^{20}$ +210·5°) was not raised by repeated crystallisation from ethyl acetate; no mutarotation was observed. Extraction of a chloroform solution of the salt with dilute ammonia solution gave an optically inactive solution of the ammonium salt.

4-Substituted 2-Acetomethylamido-4′-methyldiphenyl Sulphones.—The appropriate *o*-nitroaryl halides were condensed with sodium *p*-tolylsulphide, the thio-ethers were oxidised (hydrogen peroxide in acetic acid) to sulphones, and the nitro-groups then reduced to amino-groups with stannous chloride in aqueous-alcoholic hydrochloric acid. Acetylation of the amino-sulphones, followed by methylation with methyl sulphate and alcoholic sodium ethoxide, gave the required compounds. The following substituted 4′-methyldiphenyl sulphides have not previously been described: *2-nitro-4-methoxy-*, orange prisms (from methanol), m. p. 96° (Found: C, 61·3; H, 4·6. $C_{14}H_{13}O_3NS$ requires C, 61·1; H, 4·8%); *4-bromo-2-nitro-*, elongated orange prisms (from dioxan), m. p. 124° (Found: C, 48·6; H, 3·3. $C_{13}H_{10}O_2NBrS$ requires C, 48·2; H, 3·1%). The following substituted 4′-methyldiphenyl sulphones are also new: *2-acetomethylamido-*, prisms (from alcohol), m. p. 121° (Found: C, 63·5; H, 5·0. $C_{16}H_{15}O_3NS$ requires C, 63·4; H, 5·3%); *2-acetomethylamido-4-methyl-*, needles (from alcohol), m. p. 161° (Found: C, 64·5; H, 5·7; N, 4·5. $C_{17}H_{17}O_3NS$ requires C, 64·4; H, 6·0; N, 4·5%); *2-nitro-4-methoxy-*, needles (from alcohol), m. p. 127° (Found: C, 54·8; H, 4·2. $C_{14}H_{13}O_5NS$ requires C, 54·8; H, 4·2%); *2-amino-4-methoxy-*, small needles (from benzene), m. p. 153° (Found: C, 60·7; H, 5·5. $C_{14}H_{15}O_3NS$ requires C, 60·7; H, 5·4%); 2-acetamido-4-methoxy-, needles (from alcohol), m. p. 115°; *2-acetomethylamido-4-methoxy-*, prisms (from methanol), m. p. 147° (Found: C, 61·3; H, 5·8; N, 4·4. $C_{17}H_{19}O_4NS$ requires C, 61·3; H, 5·7; N, 4·2%); *4-chloro-2-amino-*, white platelets (from alcohol), m. p. 137° (Found: C, 55·6; H, 4·3. $C_{13}H_{12}O_2NClS$ requires C, 55·4; H, 4·3%); *4-chloro-2-acetamido-*, needles (from methanol), m. p. 129° (Found: C, 55·8; H, 4·3. $C_{15}H_{14}O_3NClS$ requires C, 55·7; H, 4·3%); *4-chloro-2-acetomethylamido-*, prisms (from acetic acid), m. p. 175° (Found: C, 57·1; H, 4·6; N, 4·3. $C_{16}H_{16}O_3NClS$ requires C, 56·9; H, 4·8; N, 4·2%); *4-bromo-2-nitro-*, white needles (from alcohol), m. p. 132° (Found: C, 43·9; H, 2·9. $C_{13}H_{10}O_4NBrS$ requires C, 43·8; H, 2·8%); *4-bromo-2-amino-*, prisms (from alcohol), m. p. 154° (Found: C, 47·7; H, 3·8. $C_{13}H_{12}O_2NBrS$ requires C, 47·9; H, 3·7%); *4-bromo-2-acetamido-*, white prisms (from methanol), m. p. 132° (Found: C, 49·0; H, 4·1. $C_{15}H_{14}O_3NBrS$ requires C, 49·0; H, 3·8%); *4-bromo-2-acetomethylamido-*, white prisms (from alcohol), m. p. 160° (Found: C, 50·2; H, 4·2; N, 4·0. $C_{16}H_{16}O_3NBrS$ requires C, 50·3; H, 4·2; N, 3·7%).

4-Substituted 2-Acetomethylamido-4′-methyldiphenyl Sulphones in Ethyl (+)-Tartrate.—Solutions of the compounds (2 g.) in the ester (15 c.c.) were kept at room temperature for several hours, and the solute then recovered by precipitation with water. In each case the recovered material was optically inactive. The unsubstituted sulphone (IV; X = H) (2 g.) was crystallised from ethyl (+)-tartrate (5 c.c.). Both the crystals which separated and the material remaining in the mother-liquors were optically inactive in chloroform solution.

4-Nitro-2-acetomethylamido-4′-methyldiphenyl Sulphide.—2-Chloro-5-nitro-*N*-methylacetanilide was condensed with sodium *p*-tolyl sulphide; the *sulphide* formed dull yellow prisms, m. p. 157° from alcohol, (Found: C, 60·8; H, 5·1. $C_{16}H_{16}O_3N_2S$ requires C, 60·8; H, 5·1%). Oxidation with hydrogen peroxide in acetic acid gave the *sulphone*, white platelets (from alcohol), m. p. 171° (Found: C, 55·3; H, 4·6. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6%). The latter compound was crystallised from ethyl (+)-tartrate; both the crystals and the material recovered from the mother-liquors were optically inactive.

Methyl 2-Chloro-N-benzoyl-6′-methyldiphenylamine-2′-carboxylate (prisms, m. p. 169°) *in Asymmetric Solvents*.—(a) *Ethyl (+)-tartrate*. The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). Crystals: 1·1022 g. in 15 c.c. of chloroform had α^{20} −0·11°, rising to zero, half-life period = 8 minutes. Precipitate: 0·4623 g. in 15 c.c. of chloroform had α^{20} −0·27°, rising to zero, half-life period = 8 minutes. A solution of the compound (2 g.) in ethyl (+)-tartrate (20 c.c.) was kept for several hours, and the solute precipitated by addition of water; 1·0899 g. in 15 c.c. of chloroform had α^{20} −0·32°, rising to zero, half-life period = 8 minutes.

(b) *Ethyl (−)-tartrate*. The compound (3 g.) was recrystallised from ethyl (−)-tartrate (8 c.c.). Crystals: 1·322 g. in 15 c.c. of chloroform had α^{21} +0·14°, falling to zero in 30 minutes. Precipitate: insufficient for examination.

Methyl 4:6-Dichloro-N-benzoyldiphenylamine-2-carboxylate (prisms, m. p. 119°) in *Ethyl (+)-Tartrate*.—The compound (3 g.) was crystallised from ethyl (+)-tartrate (9 c.c.). Crystals: 20·25 g. in 15 c.c. of chloroform had α^{19} −0·09°, rising to zero, half-life period = 5 minutes. Precipitate: 0·57 g. in 15 c.c. of chloroform had α^{19} −0·03°, rising to zero. A solution of the compound (2 g.) in ethyl (+)-tartrate (20 c.c.) was kept for 24 hours, and the solute precipitated with water; 1·55 g. in 15 c.c. of chloroform had α^{20} −0·11°, rising to zero.

N-o-Chlorophenylbenzimino o-carbomethoxyphenyl ether prisms (from methanol), m. p. 89° (Found: C, 68·6; H, 4·4. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4%), and *methyl 2-chloro-N-benzoyldiphenylamine-2′-carboxylate*, prisms, m. p. 123° (Found: C, 68·9; H, 4·5. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4%), were prepared.

Methyl 2-Chloro-N-benzoyldiphenylamine-2′-carboxylate in Ethyl (+)-Tartrate.—The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). The crystals were optically inactive. Precipitate: 1·653 g. in 15 c.c. of chloroform had α^{19} −0·15°, rising to zero, half-life period = 15 minutes.

A solution of the compound (1 g.) in ethyl (+)-tartrate (5 c.c.) was kept for several hours, and the solute precipitated : 0·955 g. in 15 c.c. of chloroform had α^{19} −0·16°, rising to zero.

Crystallisation of α-Benzyldeoxybenzoin from Ethyl (+)-Tartrate.—α-Benzyldeoxybenzoin (30 g.) was crystallised from ethyl (+)-tartrate (170 c.c.) to give crystals, $[\alpha]^{20}$ −2·11° (*c*, 5 in chloroform), which were then crystallised from more tartrate (200 c.c.) and then successively from four 80-c.c. portions; the succeeding fractions had $[\alpha]^{20}$ −2·3°, −3·8°, −5·2°, −5·7°, −5·7°, −5·7°. The α-benzyldeoxybenzoin recovered from the mother-liquors of the first three crystallisations was combined and crystallised from ethyl (+)-tartrate (30 c.c.) to give crystals (5·8 g.), $[\alpha]^{20}$ +5·7° (*c*, 5 in chloroform), and a precipitate from the mother-liquors (0·3 g.), $[\alpha]^{19}$ +17° (*c*, 2 in chloroform). In a parallel experiment with a different sample of ethyl (+)-tartrate a less soluble fraction was obtained, having $[\alpha]^{20}$ −20°; the soluble fraction had $[\alpha]^{21}$ +20°. The sample, $[\alpha]^{19}$ +17° (0·5 g.), was recrystallised from alcohol (20 c.c.); the crystals (0·3 g.) had $[\alpha]^{20}$ +5·8°, and the material recovered from the mother-liquors had $[\alpha]^{20}$ +30·9°. Similarly, the lævorotatory material of $[\alpha]^{21}$ −20° gave crystals of $[\alpha]^{20}$ −14° and a precipitate from the mother-liquors of $[\alpha]^{20}$ −34°. Owing to the small amount of material available it was not possible to carry this separation further. An attempt at separation by chromatographic analysis of a benzene solution of the active material on a column of activated alumina was unsuccessful.

Benzyl α-Benzyldeoxybenzoin-2-carboxylate.—Methyl deoxybenzoin-2-carboxylate (32 g.) was dissolved in methanol (60 c.c.) containing sodium (5·1 g.) and alkylated with benzyl chloride (29 g., 2 mols.). The *benzyl* ester formed large white needles, m. p. 75° (Found : C, 83·1; H, 5·6. $C_{29}H_{26}O_3$ requires C, 82·9; H, 5·7%). Hydrolysis gave the *acid*, white prisms (from acetic acid), m. p. 171° (Found : C, 79·7; H, 5·4. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5%).

Brucine (+)-α-Benzyldeoxybenzoin-2-carboxylate.—Brucine (16·6 g.) and the foregoing acid (11·3 g.) were dissolved in ethyl acetate (80 c.c.); the crystals which separated on cooling had $[\alpha]^{20}$ −15·3° (*c*, 5 in chloroform). Three crystallisations from ethyl acetate (200 c.c.) gave 7 g. of salt with $[\alpha]^{20}$ −12·1°.

(+)-α-Benzyldeoxybenzoin-2-carboxylic acid obtained by decomposition of the brucine salt with dilute hydrochloric acid had $[\alpha]^{20}$ +27·5° (*c*, 5 in chloroform). The *methyl* ester, obtained by esterification with excess of diazomethane, had $[\alpha]^{20}$ +29·3° (*c*, 4 in methanol), and, after 48 hours' refluxing in methanol, $[\alpha]^{20}$ +31·8° (*c*, 3 in methanol). The ester formed prisms, m. p. 110° (Found : C, 80·0; H, 5·7. $C_{23}H_{20}O_3$ requires C, 80·3; H, 5·8%).

Racemisation of (+)-α-Benzyldeoxybenzoin-2-carboxylic Acid.—A sample of the acid, $[\alpha]^{20}$ +4·85°, was heated at 100° for 33 hours with excess of aqueous-alcoholic sodium ethoxide; it was then optically inactive (*c*, 2 in chloroform). On crystallisation of some of the same sample of acid from acetic acid the crystals were found to be optically inactive (*c*, 2 in chloroform).

Methyl α-Benzyldeoxybenzoin-2-carboxylate in Ethyl (+)-Tartrate.—On crystallisation of the ester (4·7 g.) from ethyl (+)-tartrate (9 c.c.) both the crystals and the precipitate from the mother-liquors were optically inactive (*c*, 8 in chloroform).

αα'-Dinitrodibenzyl.—This was prepared by Schmidt's method (*Ber.*, 1901, **34**, 3540). From 30 g. of stilbene were obtained 12 g. of the higher-melting isomer, m. p. 235°, and 7 g. of the lower-melting isomer, m. p. 142—146°.

αα'-Dinitrodibenzyl in Ethyl (+)-Tartrate.—(a) *High-melting isomer.* This compound (2 g.) was recrystallised from ethyl (+)-tartrate (45 c.c.), some nitrogen dioxide being evolved. Crystals : 0·9467 g. in 15 c.c. of nitrobenzene had α^{20} −0·28°, rising to zero in an hour. When this experiment was repeated with 3 g. of the solute in 60 c.c. of ester, care being taken to avoid decomposition, no optical activity was detected in the crystals even when crystallisation was slow (solution kept in a bath of water slowly cooled from 84° to room temperature).

(b) *Low-melting isomer.* The compound (2 g.) was recrystallised from ethyl (+)-tartrate (10 c.c.) below 140° (conversion into the other isomer takes place above 152°); both the crystals and the material recovered from the mother-liquors were optically inactive and melted at 147°.

We wish to thank Mr. J. M. L. Cameron and Miss R. H. Kennaway who carried out the microanalyses, also the Department of Scientific and Industrial Research for a maintenance grant to one of us (S. H. G.), during the tenure of which part of this work was carried out.

UNIVERSITY OF GLASGOW. [*Received, September 21st*, 1949.]

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99. *The Reaction between Amines and 1-Chloro-2 : 4-dinitrobenzene.*

By O. L. BRADY and F. R. CROPPER.

The reaction of a number of alkylamines and dialkylamines with chlorodinitrobenzene has been studied kinetically, and it has been found that there is a remarkable difference between the rate constants for different amines which is not directly related to their basic strength; for example, the rate constant for dimethylamine is more than 30,000 times that for diisopropylamine though the latter is the stronger base.

Evidence is adduced that a steric effect plays an important part in determining the rate constant.

THE reaction between primary and secondary amines and 1-chloro-2 : 4-dinitrobenzene

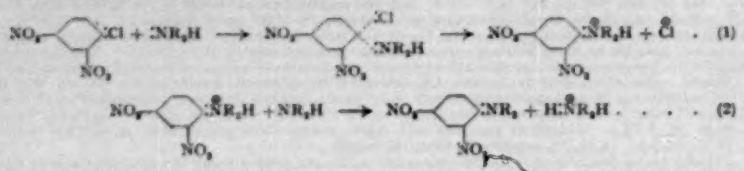
$$2NHRR' + C_6H_3Cl(NO_2)_2 \longrightarrow C_6H_3(NO_2)_2{\cdot}NRR' + NH_2RR'Cl$$

produces only the substituted dinitroaniline and amine hydrochloride. The dinitrophenylalkylamine or dinitrophenyldialkylamine does not react further with the chlorodinitrobenzene,

and the hydrolysis or alcoholysis of the last-named compound is not appreciable. The reaction, therefore, has advantages for the study of the reactivity of amines.

A concentration of amine twice that of the chlorodinitrobenzene being used, the reaction, in alcohol, was found to be of the second order, and good rate constants (k_2) were obtained for all amines used except those which reacted very slowly.

The simplest method of representing the reaction is as a heterolytic, nucleophilic one of type (*b*) in Ingold's classification of the mechanisms of substitution at a saturated carbon atom (I) (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 604), followed by loss of proton from the first product to a second molecule of amine.



Since the dinitrophenyldialkylamines are very weak bases the rate-determining reaction will be (1).

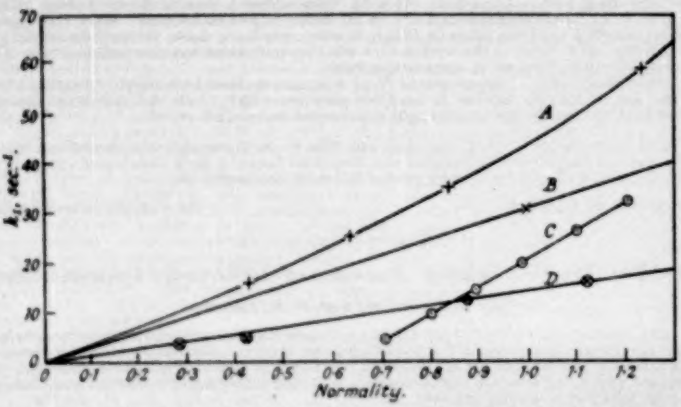
Possible secondary reactions are the following:

$$NHR_2 + HOEt \rightleftharpoons \overset{\oplus}{N}H_2R_2 + \overset{\ominus}{O}Et$$

$$(NO_2)_2C_6H_3Cl + \overset{\ominus}{O}Et \longrightarrow (NO_2)_2C_6H_3\text{·}OEt + \overset{\ominus}{Cl}$$

$$(NO_2)_2C_6H_3\text{·}OEt + NHR_2 \longrightarrow (NO_2)_2C_6H_3\text{·}NR_2 + HOEt$$

Although alkoxyl ions act readily on 1-chloro-2:4-dinitrobenzene (Holleman and ter Weel, *Rec. Trav. chim.*, 1915, **35**, 1), their concentration under the conditions used cannot be sufficiently high for interference except in the cases of very slow-acting, fairly strongly basic amines such as *tert.*-butylamine or di*iso*propylamine (see Table I) since with a concentration of triethylamine ($K_b = 6{\cdot}4 \times 10^{-4}$) some twenty times that of the amine used in the study of the second-order reaction the liberation of chloride ion is exceedingly slow.



A, B, C, Concn. *of* NH_2Me. D. Concn. *of* NEt_3, *added to* 0·64N-NH_2Me.

When the concentration of amine was far greater than that of the chlorodinitrobenzene the reaction became one of the first order or pseudo-unimolecular. The plot of the rate constant against concentration of amine is, however, not linear, the rate constant increasing more rapidly at higher concentrations of amines. The figure shows the plot of k_1^{obs} against concentration of methylamine (*A*), the concentration of chlorodinitrobenzene being 0·329N., and of k_1' calculated

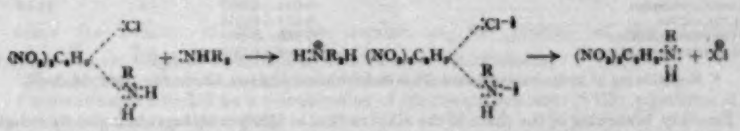
from the second-order rate constant k_2^{NH} by putting b, the concentration of methylamine, equal to unity (B).

Above 0·4N-methylamine the difference between the observed rate constant k_1 and the extrapolated value k_1' is proportional to the excess of methylamine over 0·4N. Curve C shows the plot of $k_1 - k_1'$ against concentrations of methylamine. One would expect this proportionality not to hold for concentrations of methylamine much below 0·4N., since this represents only six times the equivalent concentration of amine (0·0658N.) for the chlorodinitrobenzene, and the assumption necessary for using first-order kinetics is becoming of doubtful validity.

Triethylamine, which does not react to an appreciable extent with chlorodinitrobenzene under the conditions of experiment, also increases the rate constant when added to a reaction mixture containing 0·64N-methylamine, and the increase in the rate constant ($k_1'' - k_1$) is proportional to the concentration of triethylamine. Curve D shows ($k_1'' - k_1$)/(concn. of NEt_3).

It is clear, therefore, that the velocity is influenced by a proton acceptor. Since the dinitrophenylalkylamines are very weak bases whose salts are practically completely hydrolysed in aqueous or alcoholic solution, reaction (2) is probably extremely rapid and we have to look elsewhere for the influence of the proton acceptor.

In the intermediate stage of (1) the presence of a proton acceptor will increase the electron availability of the nitrogen and facilitate its attachment to the carbon with the accompanying extrusion of the chloride ion :



This effect will be appreciable, probably, only when the concentration of amine is relatively high as in the pseudo-unimolecular reaction.

If the mechanism suggested for the bimolecular reaction be correct, the rate constant should depend upon the electron-availability at the nitrogen of the reacting amine, and electron-donating groups therein should increase the rate constant, which one would expect to bear a direct relation to the dissociation constants of the amine. The bimolecular rate constants (k_2^{NH}) of the interaction between a number of amines with 1-chloro-2 : 4-dinitrobenzene in alcohol at 25° have been obtained by measuring the rate of liberation of chloride ion; the results are given in Table I, Col. 3.

The experimental part of this work was completed in 1935 and it was not until the results for the second-order reaction had been practically completed that it was discovered that Blanksma and Schreinemakers (*Rec. Trav. chim.*, 1933, **52**, 498) had published the rate constants for the reaction between 1-chloro-2 : 4-dinitrobenzene and a number of amines also in alcohol at 25° as measured by the rate of disappearance of amine. These are given in Table I, Col. 2, calculated to sec.$^{-1}$ from Blanksma and Schreinemakers's figures to min.$^{-1}$. Where the same amines were employed the results in Col. 2 and Col. 3 were obtained by different methods quite independently and the agreement in most cases is close. Even where there are appreciable discrepancies, *e.g.*, for piperidine, it does not affect the order of reactivity of the amines.

From a consideration of these results certain peculiarities are at once apparent. First, although the replacement of hydrogen by methyl, with the corresponding increase in basicity of the amine, leads to an increase in the rate constant ($k_2 \times 10^4$, $NH_3 = 0{\cdot}04$, $NH_2Me = 31{\cdot}6$, $NHMe_2 = 355$), yet in other cases the rate constants bear no obvious relation to the dissociation constants (K_b) of the amines. [The dissociation constants taken from the literature and given in Table I are for aqueous solutions, but it has been shown that their relative order is unchanged in passing from water to alcohol although their magnitude is greatly reduced (Goodhue and Hixon, *J. Amer. Chem. Soc.*, 1934, **56**, 1329).]

Secondly, one notices the high rate constant for methylamine ($k_2 \times 10^4 = 31{\cdot}6$) compared with ethylamine ($k_2 \times 10^4 = 9{\cdot}1$), for dimethylamine ($k_2 \times 10^4 = 355$) compared with diethylamine ($k_2 \times 10^4 = 1{\cdot}9$), and for piperidine ($k_2 \times 10^4 = 153$) compared with ethyl-*n*-propylamine ($k_2 \times 10^4 = 1{\cdot}7$) and α-pipecoline ($k_2 \times 10^4 = 0{\cdot}22$).

Thirdly, whereas the rate constant for dimethylamine is about ten times that for methylamine, the rate constant for diethylamine is about one-fifth of that for ethylamine, and that for di*iso*propylamine about one-hundredth of that for *iso*propylamine.

TABLE I.

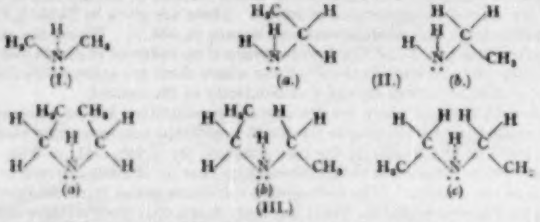
Amine.	$10^4 k_2^{25}$, sec.$^{-1}$, B. & Schr.	$10^4 k_2^{25}$, sec.$^{-1}$, B. & C.	$10^4 K_b$.	pK_B (25°).*
Dimethylamine	348	355	5·0	10·71
Piperidine	191	153	12·5	11·13
Methylamine	31·3	31·6	4·0	10·64
n-Heptylamine	10·2	10·0	—	—
n-Amylamine	10·1	—	—	10·84
n-Butylamine	9·5	10·0	—	10·61
n-Propylamine	8·9	9·6	3·9	10·58
Ethylamine	8·6	9·2	4·6	10·67
*iso*Butylamine	—	6·8	2·6	10·42
Diethylamine	1·8	1·9	10·0	10·98
Di-n-butylamine	—	1·8	—	11·31
Di*iso*amylamine	1·7	—	—	11·00
Ethyl-n-propylamine	—	1·7	—	—
Di-n-propylamine	1·6	1·6	8·2	10·91
*iso*Propylamine	1·1	1·0	4·3	10·63
sec.-Butylamine	0·92	0·91	3·6	10·56
Di*iso*butylamine	0·67	0·58	3·9	10·62
α-Pipecoline	—	0·22	—	10·98
Ethyl*iso*propylamine	—	0·18—0·033	—	—
Ammonia	0·04	0·04	0·18	9·27
tert.-Butylamine	—	0·038	3·4	10·45
Di*iso*propylamine	—	0·011—0·007	—	11·05
αα-Lupetidine	—	0·011—0·006	—	—
Tetrahydroquinoline	—	0·068—0·004	—	—
Tetrahydroquinaldine	—	0·004—0·002	—	—

* Negative log of hydrolysis constant (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469).

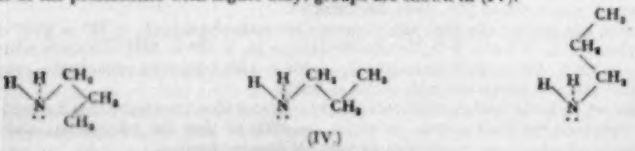
Fourthly, branching of the chain of the alkyl radical at the first carbon atom greatly reduces the rate constant ($k_2 \times 10^4$, n-propylamine = 9·6, *iso*propylamine = 1·0; n-butylamine = 10·0, *sec.*-butylamine = 0·92, *tert.*-butylamine = 0·038), but there is much less difference between n-butylamine ($k_2 \times 10^4 = 10·0$ and *iso*butylamine ($k_2 \times 10^4 = 6·8$).

In the light of these results it seems that the arrangement in space of the atoms of the alkyl groups in the amines plays an important part in determining their reactivity towards chlorodinitrobenzene.

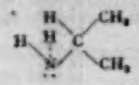
If one considers the stereochemistry of methylamine and ethylamine it will be seen that, whereas in methylamine and dimethylamine (I) there is at all times ample room for the approach of the large chlorodinitrobenzene molecule to the exposed part of the nitrogen atom, yet in the case of ethylamine, if there is free rotation about the carbon–nitrogen bond, at some time the methyl group can interfere with the approach of the chlorodinitrobenzene (II*b*). With diethylamine the time during which this steric hindrance will be effective will be greater (III*b*, III*c*).



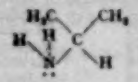
Some of the possibilities with higher alkyl groups are shown in (IV).

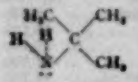


Branching at the first carbon atom of the alkyl chain will increase the time during which steric hindrance is effective; in *iso*propylamine (V) the time at which a methyl will exert a steric hindrance will be twice that in ethylamine, whilst in *tert.*-butylamine (VI) a methyl group will at all times interfere.



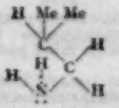
(V.)



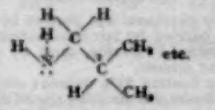


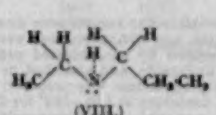
(VI.)

The effect of two *iso*propyl groups would be greater than that of one. The methyl in the *iso*butyl group would not have the same effect (VII), and isobutylamine might be expected to show similar results to n-butylamine.



(VII.)



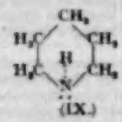


(VIII.)

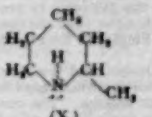
Since the basicity of the amine depends on the position of the equilibrium $NH_2R + \overset{\oplus}{H} \rightleftharpoons \overset{\oplus}{N}H_2R$, it would not be affected by steric influences.

The rate constants are all in agreement with the above views.

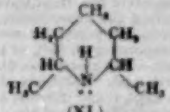
Confirmation is afforded by a consideration of ethyl-n-propylamine (VIII), piperidine (IX), pipecoline (X), and lupetidine (XI).



(IX.)



(X.)



(XI.)

In the first case the rate constant is low ($k_2 \times 10^4 = 1{\cdot}7$) and of the order of that for diethylamine, since at some time a steric effect can be exerted; when the carbon atoms take part in ring formation the state of affairs shown in (VIII) cannot occur and the rate constant for piperidine ($k_2 \times 10^4 = 153$) is of the same order as that of dimethylamine; the introduction of a permanently hindering methyl group results in a greatly reduced rate constant for α-pipecoline ($k_2 \times 10^4 = 0{\cdot}22$). Lellmann (*Ber.*, 1890, **23**, 1388; 1891, **24**, 2104) observed qualitatively the abnormally slow rate of reaction of α-pipecoline with 1-chloro-2 : 4-dinitrobenzene compared with that of piperidine or β-pipecoline (the β-methyl group could not interfere sterically). Finally, the rate constant for αα-lupetidine, where there are two permanently hindering methyl groups, is so low ($k_2 \times 10^4 = 0{\cdot}011$—$0{\cdot}006$) as to prevent accurate measurement at the temperature employed for the other amines.

The foregoing explanation has been put forward on the assumption that perfectly free rotation exists about the carbon–nitrogen bond, but the study of the Raman spectra of, *e.g.*, such a compound as 1 : 2-dichloroethane, has suggested that there is some restriction of rotation even between two singly bound carbon atoms. The possibility that the terminal methyl group in ethylamine is preferentially situated near the exposed part of the nitrogen atom cannot be rejected; it might certainly be so if the polarity of the C–H bond in the alkylamines is in the direction $\overset{\oplus}{C}$–$\overset{\ominus}{H}$ but, as stated by Gent (*Quart. Reviews*, 1948, **2**, 381), knowledge of the polarity of the C–H bond in various situations is still small, so it would be unprofitable to speculate in this direction.

The rate constants for the bimolecular reaction between chlorodinitrobenzene and methylamine and dimethylamine have been determined at 25°, 30°, 35°, and 40°, and it was found that the plot of log k against $1/T$ was, in both cases, a straight line, so it was assumed that the Arrhenius equation held for the interaction of the other amines with chlorodinitrobenzene. The energies of activation and collision frequencies are given in Table II. With the exception of

those for methylamine and dimethylamine, the results are probably not very accurate, as measurements were made at only two temperatures.

TABLE II.

Amine.	E, cals.	$B \times 10^{-6}$, sec.$^{-1}$.	Amine.	E, cals.	$B \times 10^{-6}$, sec.$^{-1}$.
Dimethylamine	9,340	1·7	Ethylpropylamine ...	13,900	5·8
Piperidine	10,200	4·7	Di-*n*-butylamine ...	14,200	48
Methylamine	10,700	2·3	*sec.*-Butylamine	14,800	67
Ethylamine	11,700	3·6	Di*iso*butylamine	14,800	42
n-Butylamine	11,700	3·9	*iso*Butylamine	15,500	1600
Diethylamine	12,650	3·7	*iso*Propylamine	15,900	475

The energies of activation are low and rise with the decline in the rate constant, but *iso*butylamine and to a smaller degree *iso*propylamine are exceptions.

EXPERIMENTAL.

Materials.—The amines were mostly purchased and purified by careful fractionation; methylamine, ethylamine, and dimethylamine were purified by recrystallisation of their hydrochlorides; the bases were liberated by concentrated potassium hydroxide, dried by passing through tubes packed with sodium hydroxide, and absorbed in the solvent.

Ethylpropylamine was prepared by heating 33% aqueous ethylamine with *n*-propyl chloride in a rotating autoclave at 125—150° for 24 hours and distilling the oil liberated by alkali; the fraction, b. p. 84—86°, was used. Ethyl*iso*propylamine was prepared similarly by using *iso*propyl bromide at 120—160° for 120 hours, the fraction of b. p. 70—74° being used. *tert.*-Butylamine was prepared by the Hofmann reaction on pivalamide and purified through the hydrochloride and by distillation, the fraction, b. p. 45—46°, being used. α-Pipecoline, αα-lupetidine, and tetrahydroquinaldine were prepared by reduction of α-picoline, αα-lutidine, and quinaldine; α-pipecoline was purified through the thiocarbamate (Ladenberg, *Annalen*, 1888, **247**, 62) and collected at 199°; αα-lupetidine was purified through its hydrochloride and collected at 127°; tetrahydroquinaldine was purified by the method of Pope and Peachey (*J.*, 1899, **75**, 1089) and collected at 154°/43 mm.

The 1-chloro-2 : 4-dinitrobenzene was crystallised from benzene. No attempt was made to employ alcohol completely free from water owing to the difficulty in preventing absorption of small quantities of water during the experiments. It was thought that changes in velocity would be greater as the alcohol approached purity, so one batch was employed for all experiments; this had a density of 0·788 at 25°, corresponding to 99% of alcohol.

Procedure.—The amine was dissolved in alcohol, and the strength and the concentration checked by titration with acid. Solutions of 1-chloro-2 : 4-dinitrobenzene were prepared by dissolving a weighed quantity in alcohol and dilution to the correct volume. The concentrations of chlorodinitrobenzene at time 0 were 0·0329N. or 0·0148N., obtained by using 25 c.c. of 0·986N- or 0·0444N-chlorodinitrobenzene. The concentrations of the amines at time 0 were 0·0658N. or 0·0296N., obtained by using 50 c.c. of 0·0986N or 0·0444N-amine. In these cases the concentration of amine was twice that of the chlorodinitrobenzene. Where excess of amine was used the concentrations varied from 0·2N. to 1·5N., obtained by using 50 c.c. of 0·3N- to 2N-amine.

In carrying out the reaction, 50 c.c. of the amine solution at 25° were mixed with 25 c.c. of the chlorodinitrobenzene solution, also at 25°, and the mixture was kept in a closed vessel in a thermostat. At known intervals 10 c.c. of the reaction mixture were removed with a pipette and run into a mixture of 5 c.c. of nitric acid and 25 c.c. of 0·017N-silver nitrate in a 100-c.c. measuring flask. The volume was made up to 100 c.c. with water, the whole filtered, and 50 c.c. of the filtrate were titrated with a standard solution of potassium thiocyanate, ferric alum being used as indicator.

For tetrahydroquinoline and tetrahydroquinaldine the above method could not be used owing to the formation of an intense red colour with ferric alum and nitric acid, so the excess of silver nitrate was titrated with potassium iodide, starch–nitrite indicator being used.

Results.

The Bimolecular Reaction.—Figures are given below for the bimolecular reaction, in some detail for methylamine, dimethylamine, and ethylamine, to indicate the agreement between the values found, and in summarised form for the other amines (Table III). In each case samples were taken at five or six time intervals and the variation in the constant was small in the more rapid reactions. In the very slow reactions, *e.g.*, *tert.*-butylamine, the constant diminished with time, and greater detail is given of this determination as an example.

Since two moles of amine to one of chlorodinitrobenzene were used and two moles of amine react with one mole of chlorodinitrobenzene, if a = concn. of chlorodinitrobenzene, $2a$ = concn. of amine then $dx/dt = k_2(a - x)(2a - 2x) = 2k_2(a - x)^2 = K(a - x)^2$; hence $K = x/ta(a - x)$, where $K = 2k_2$.

Methylamine.

0·0658N-NH_2Me, 0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time (secs.)	630	1800	3600	6030	9960	17,460
Decompn., %	13·56	27·76	43·83	57·12	68·49	79·39
$k_2 \times 10^4$	34·6	32·5	34·1	33·6	33·2	33·5

50% Decompn. at 4620 secs. Average $k_2 = 33·6 \times 10^{-4}$ sec.$^{-1}$.

0·0296*N*-NH_2Me, 0·0148*N*-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time (secs.)	1500	3150	4960	5790	12,810	84,240
Decompn., %	12·1	22·2	31·2	35·0	54·2	88·6
$k_2 \times 10^4$	31·0	30·6	30·7	31·4	31·2	31·6

50% Decompn. at 10,620 secs. Average $k_2 = 31·1 \times 10^{-4}$ sec.$^{-1}$.
$t_1/t'_1 = 2·3$; ratio of concentrations 0·0329/0·0148 = 2·22.
The average of four determinations gave $k_2 = 31·6 \times 10^{-4}$ sec.$^{-1}$.

0·0658*N*-NH_2Me, 0·0329*N*-$C_6H_3Cl(NO_2)_2$, in 99% alcohol.

At 30°.			At 35°.			At 40°.		
Time, secs.	Decompn., %	$k_2 \times 10^4$.	Time, secs.	Decompn., %	$k_2 \times 10^4$.	Time, secs.	Decompn., %	$k_2 \times 10^4$.
900	20·7	44·2	1005	28·06	58·9	660	25·3	78·1
1800	33·76	43·1	1500	36·75	59·1	900	31·66	78·3
3000	46·0	43·2	3615	57·91	57·9	1200	38·41	79·1
4200	54·88	44·1	5820	69·41	59·3	1920	50·24	80·0
5400	60·36	42·2	8925	77·68	59·3	3000	61·43	81·3
7380	67·96	43·7				4500	70·49	80·7
	Average =	43·4		Average =	58·9		Average =	79·6

Dimethylamine.

0·0658*N*-$NHMe_2$, 0·0329*N*-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, secs.	240	360	600	1686	2490
Decompn., %	35·23	45·67	58·72	80·11	85·65
$k_2 \times 10^4$	345	355	360	363	372

50% Decompn. at 435 secs. Average $k_2 = 359 \times 10^{-4}$ sec.$^{-1}$.

0·029*N*-$NHMe_2$, 0·0148*N*-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, secs.	555	1290	2160	4890
Decompn., %	36·5	56·2	69·0	84·1
$k_2 \times 10^4$	362	357	348	366

50% Decompn. at 975 secs. Average $k_2 = 351 \times 10^{-4}$ sec.$^{-1}$.
Ratio $t_1/t'_1 = 2·24$; ratio of concentrations = 2·22.

0·0658*N*-$NHMe_2$, 0·0329*N*-$C_6H_3Cl(NO_2)_2$, in 99% alcohol.

At 30°.			At 35°.			At 40°.		
Time, secs.	Decompn., %	$k_2 \times 10^4$.	Time, secs.	Decompn., %	$k_2 \times 10^4$.	Time, secs.	Decompn., %	$k_2 \times 10^4$.
180	35·09	45·6	90	22·06	57·5	90	31·66	78·2
240	42·20	46·2	105	28·46	57·6	162	45·16	77·3
306	48·54	46·9	225	46·41	58·4	210	50·24	78·7
390	54·44	46·6	270	52·38	62·0	240	55·31	78·4
570	63·74	46·9	300	54·69	61·2	303	60·78	77·8
774	70·08	46·1	480	65·26	59·6	420	68·38	78·3
	Average	46·4		Average	59·4		Average	78·1

Ethylamine.

0·0658*N*-NH_2Et, 0·0329*N*-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, secs.	3825	9825	17,685	26,820	40,170	87,780
Decompn., %	19·16	37·69	50·93	62·42	69·9	83·72
$k_2 \times 10^4$	9·4	9·3	8·9	8·8	8·8	8·9

50% Decompn. at 12,620 secs. Average $k_2 = 9·1 \times 10^{-4}$ sec.$^{-1}$.

0·0296*N*-NH_2Et, 0·0148*N*-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, secs.	6885	21,420	38,430	84,605	258,420
Decompn., %	16·0	36·5	50·6	69·7	87·6
$k_2 \times 10^4$	9·3	9·2	9·0	9·2	9·2

50% Decompn. at 36,600 secs. Average $k_2 = 9·2 \times 10^{-4}$ sec.$^{-1}$.
Ratio $t_1/t'_1 = 2·20$; ratio of concentrations = 2·22.

0·0658*N*-NH_2Et, 0·0329*N*-$C_6H_3Cl(NO_2)_2$; 35°; in 99% alcohol.

Time, secs.	1850	4500	6770	10,440	14,100	17,700
Decompn., %	17·9	34·0	47·33	54·68	62·04	66·64
$k_2 \times 10^4$	17·2	17·4	17·6	17·6	17·6	16·7

Average $k_2 = 17·4 \times 10^{-4}$ sec.$^{-1}$.

tert.-Butylamine.

0·0296N-NH_2Bu^t, 0·0148N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, hours	172·3	312·2	552·7	1206·2	1802·1	2502·2
Decompn., %	8·27	16·4	19·2	32·8	38·9	49·1
$k_2 \times 10^4$	0·0049	[0·0059]	0·0040	0·0035	0·0023	0·0034

Average $k_2 = 0·0038 \times 10^{-4}$ sec.$^{-1}$.

Time, hours	165·6	378·1	594	1483·6	2130·4	4027
Decompn., %	8·27	16·43	21·4	36·9	44·0	59·4
$k_2 \times 10^4$	0·0051	0·0049	0·0043	0·0037	0·0035	0·0034

Average $k_2 = 0·0041 \times 10^{-4}$ sec.$^{-1}$.

Diisopropylamine.

0·0658N-$NHPr^i_2$, 0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, mins.	15,880	30,223	67,940	85,117	110,860	286,689
Decompn., %	6·86	11·46	17·00	19·76	23·89	43·19
$k_2 \times 10^4$	0·012	0·011	0·0078	0·0073	0·0072	0·0067

Lupetidine.

0·0658N-Lupetidine, 0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, mins.	15,774	34,537	70,629	92,240	136,808	156,852
Decompn., %	6·41	12·96	18·73	20·66	25·66	32·15
$k_2 \times 10^4$	0·011	0·011	0·0082	0·0072	0·0064	0·0063

In the case of amines which react less rapidly than ammonia, *e.g.*, *tert.*-butylamine, *diiso*propylamine, and lupetidine (cf. above), there is a fall in the rate constant, rapid at first but then much slower. Probably these amines contain small amounts of more reactive amines which are removed in the first period of the reaction. With these very slowly reacting amines very small quantities of impurities would have a large effect in the first stage.

The Pseudo-unimolecular Reaction.—The results obtained are summarised in Table IV.

Addition of Triethylamine.—With 0·0329N-chlorodinitrobenzene and N-triethylamine in alcohol at 25° less than 2% of chloride ion was liberated after 6180 secs., and less than 10% after 1,737,000 secs. The results of addition of triethylamine in the first-order reaction are summarised in Table V.

TABLE III.

0·0658N-Amine, 0·0329N-$C_6H_3Cl(NO_2)_2$ in 99% alcohol.

	Temp. = 25°.		Temp. = 35°.		Average values.	
Amine.	Time, secs. × 10^{-4}.	$k_2 \times 10^4$, sec.$^{-1}$, extremes.	Time, secs. × 10^{-4}.	$k_2 \times 10^4$, sec.$^{-1}$, extremes.	$A_2^{25} \times 10^4$, sec.$^{-1}$.	$A_2^{35} \times 10^4$, sec.$^{-1}$.
n-Propylamine	396—7,418	9·4—9·8	—	—	9·6	—
n-Butylamine	160—3,543	9·8—10·1	540—1,746	18·8—19·5	10·0	19·2
n-Heptylamine	408—3,804	9·7—10·0	—	—	10·0	—
Diethylamine	1,575—17,340	1·9—1·9	780—9,426	3·7—4·0	1·9	3·8
Di-n-propylamine	1,620—43,638	1·5—1·7	—	—	1·6	—
Di-n-butylamine	1,746—28,182	1·8—1·9	1,326—10,974	3·9—4·1	1·8	4·0
Ethyl-n-propylamine	1,884—34,560	1·6—1·7	1,155—19,380	3·3—3·6	1·7	3·4
*iso*Butylamine	360—11,320	6·6—7·1	300—1,790	14·9—16·0	6·8	15·6
*iso*Propylamine	1,929—42,972	0·95—1·0	1,248—17,688	2·3—2·5	1·0	2·4
sec.-Butylamine	2,826—60,546	0·88—0·95	2,826—17,022	2·0—2·1	0·91	2·1
Diisobutylamine	630—61,020	0·56—0·60	8,940—26,710	1·3—1·4	0·58	1·3
Piperidine	42—219	153—158	22·5—136·5	264—275	153	269
α-Pipecoline	4,291 min.—44,673	0·21—0·25	—	—	0·22	—
Ammonia	4,090 min.—100,000	0·037—0·046	—	—	0·04	—
Ethyl*iso*propylamine	6,140 min.—105,066	0·014—0·0032 *				
" "	4,266 min.—126,780	0·019—0·0031 *				
Tetrahydroquinoline	3,012 min.—109,657	0·065—0·006 *				
" "	17,149 min.—161,517	0·021—0·0045 *				
Tetrahydroquinaldine	23,061 min.—119,654	0·004—0·002 *				

* In these cases there was a progressive fall of k_2 with time.

TABLE IV.

0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; 99% alcohol.

Amine.	Concn., N.	Time, secs.	Extremes of $k_1 \times 10^4$.	Average $k_1 \times 10^4$.
Methylamine	0·424	90—960	15·4—16·5	16·1
	0·634	90—1,026	25·3—26·3	25·6
	0·833	120—605	35·0—35·9	35·6
	1·227	60—420	58·2—62·8	59·4
Ethylamine	0·583	126—4,260	6·13—6·95	6·35
	0·840	150—3,120	10·3—10·8	10·5
	1·350	245—1,170	20·1—21·1	20·5
n-Propylamine	0·553	345—3,000	5·96—6·45	6·15
	0·687	630—3,570	7·81—7·85	7·66
	0·790	720—2,790	9·07—9·35	9·26
n-Butylamine	0·573	615—3,270	7·08—7·24	7·12
	0·730	330—2,850	9·08—9·84	9·37
	0·753	375—1,890	9·62—9·92	9·75
n-Heptylamine	0·700	330—2,430	9·53—9·72	9·61
Dimethylamine	0·450	64—190	177—191	183 *
	0·500	57—180	206—218	214 *
	0·580	60—180	252—260	256 *
Diethylamine	0·491	1,935—18,300	0·99—1·05	1·03
	0·573	1,935—17,280	1·21—1·28	1·22
Di-n-propylamine	0·347	1,575—39,660	0·53—0·55	0·54
	0·506	1,440—21,300	1·02—1·04	1·03
Di-n-butylamine	0·400	4,500—16,630	0·76—0·82	0·78
	0·483	2,835—24,672	0·92—0·98	0·96
	0·560	2,646—20,820	1·11—1·18	1·13
Ethyl-n-propylamine	0·373	2,340—15,750	0·67—0·71	0·69
	0·453	3,000—28,980	0·80—0·89	0·85
	0·555	3,006—20,160	1·02—1·09	1·07
*iso*Butylamine	0·640	303—1,815	5·45—5·93	5·78
	0·813	270—1,170	7·85—8·25	8·04
	1·000	1,860—4,260	10·4—11·1	10·7
*iso*Propylamine	0·647	1,515—19,110	0·86—0·92	0·88
	0·947	3,426—15,666	1·36—1·45	1·40
sec.-Butylamine	0·400	5,220—40,950	0·42—0·45	0·44
	0·600	9,000—25,200	0·50—0·52	0·52
Di*iso*butylamine	0·520	3,300—37,890	0·32—0·35	0·34
	0·650	2,703—34,260	0·44—0·46	0·45
	0·0148N-$C_6H_3(NO_2)_2Cl$; 25°.			
Methylamine	0·634	180—1,020	25·0—26·4	25·6
	0·833	126—636	36·5—38·0	37·5
	1·227	60—360	62·0—79·5	69·3

* Approximate, as the reaction is too fast at 25° for satisfactory measurements.

TABLE V.

0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Amine.	Concn. of amine, N.	Concn. of NEt_3.	Time, secs.	Extremes of $k_1 \times 10^4$.	Average $k_1 \times 10^4$.
Methylamine	0·64	0·28	90—600	28·2—29·6	29·1
	,,	0·329	90—450	30·8—31·8	31·4
	,,	0·873	150—480	36·3—40·5	38·4
	,,	1·12	66—420	38·3—43·2	42·2
	,,	1·33	75—465	44·0—46·0	44·9
	,,	2·00	66—450	56·3—59·3	58·0
Ethylamine	0·84	0·607	165—1,800	13·7—13·9	13·9
n-Propylamine	0·687	0·633	180—2,895	10·1—10·8	10·4
n-Butylamine	0·730	0·633	360—2,580	10·7—10·8	10·8
Dimethylamine	0·500	0·660	65—180	256—275	268 *
Diethylamine	0·573	0·807	930—16,020	1·64—1·85	1·72
Di-n-propylamine	0·347	0·677	3,075—39,060	0·66—0·69	0·68
Di-n-butylamine	0·483	0·660	5,820—20,820	1·13—1·16	1·15
*iso*Butylamine	0·813	0·687	420—840	9·55—10·8	10·0
*iso*Propylamine	0·947	0·647	2,580—9,210	1·85—1·96	1·91
sec.-Butylamine	0·400	0·440	8,460—30,810	0·51—0·53	0·52
Ammonia	1·093	0·647	21,546—211,620	0·082—0·089	0·088

* Approximate.

A number of derivatives of dinitroaniline have been prepared in the course of the work. The residual solutions obtained from the interaction of *tert.*-butylamine and 1-chloro-2 : 4-dinitrobenzene were mixed, heated in the water-bath, cooled, and diluted with water. The precipitate on crystallisation from dilute alcohol gave yellow crystals of *N*-tert.-*butyl*-2 : 4-*dinitroaniline*, m. p. 119° (Found : C, 50·6; H, 5·5. $C_{10}H_{13}O_4N_3$ requires C, 50·2; H, 5·5%). Chlorodinitrobenzene (5 g.) and diisopropylamine (5 g.) were heated in a sealed tube at 100° for 30 days. The black mass was extracted with boiling alcohol, and the solid which separated on cooling after being twice crystallised from alcohol gave *N*-*diisopropyl*-2 : 4-*dinitroaniline* as golden-yellow needles, m. p. 127° (Found : C, 53·9; H, 6·2. $C_{12}H_{17}O_4N_3$ requires C, 53·9; H, 6·4%). Mulder (*Rec. Trav. chim.*, 1906, **25**, 109, 113) failed to obtain this compound by this method. Alcoholic solution of α-pipecoline (100 c.c. of N/3) and chlorodinitrobenzene (75 c.c. of N/10) were mixed and kept for 14 days. The solution was evaporated to small bulk and the solid which separated on crystallisation from alcohol gave orange-red crystals of *N*-α-*pipecolyl*-2 : 4-*dinitroaniline*, m. p. 67° (Found: C, 54·3; H, 5·6. $C_{12}H_{15}O_4N_3$ requires C, 54·1; H, 5·7%); Leilman (*loc. cit.*) described an impure specimen as an oil. Alcoholic solutions of tetrahydroquinoline (60 c.c. of N.) and chlorodinitrobenzene (250 c.c. of N/10) were heated to 100° and kept for two days, evaporated to small bulk, and the solid which separated crystallised from alcohol–benzene; *N*-*tetrahydroquinolyl*-2 : 4-*dinitroaniline* was obtained as yellow crystals, m. p. 155·5°, which became red on exposure to light (Found : C, 60·6; H, 4·4. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·4%).

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THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON. [*Received, October 7th*, 1949.]

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100. *Inorganic Chromatography on Cellulose. Part II*. The Separation and Detection of Metals and Acid Radicals on Strips of Absorbent Paper.*

By F. H. BURSTALL, G. R. DAVIES, R. P. LINSTEAD, and R. A. WELLS.

A method for the separation and detection of a number of metallic ions and acid radicals by extraction with organic solvent mixtures on strips or sheets of absorbent paper is described. Detection is accomplished by spraying the strip or sheet of paper with a solution containing suitable reagents; the presence of individual metals or acid radicals is then made visible as characteristic coloured bands. The following groups of ions have been separated (R.E. = rare earths) :

(a).	(b).	(c).	(d).	(e).	(f).	(g).	(h.)	(i).	(j).
Pb^{2+}	Au^{3+}	Fe^{3+}	Ni^{2+}	Pt^{4+}	R.E.$^{3+}$	SeO_3^{2-}	Li^+	Ca^{2+}	F^-
Cu^{2+}	Sb^{3+}	Al^{3+}	Mn^{2+}	Pd^{2+}	Sc^{3+}	TeO_3^{2-}	Na^+	Sr^{2+}	Cl^-
Bi^{3+}	Sn^{2+}	Cr^{3+}	Co^{2+}	Rh^{3+}	Th^{4+}	—	K^+	Ba^{2+}	Br^-
Cd^{2+}	—	—	Zn^{2+}	Ir^{4+}	—	—	—	—	I^-
Hg^{2+}	—	—	Cu^{2+}	Ir^{3+}	—	—	—	—	—
			Fe^{3+}	Ru^{4+}					
			UO_2^{2+}	Ru^{3+}					
			VO_2^+	Os^{4+}					
			Ti^{4+}	Au^{3+}					

The ratio of the distances moved by the ion to that moved by the solvent (R_F value) has been determined in a number of cases. The significance of these measurements is discussed.

WE have already given a preliminary account of the separation of inorganic salts by the technique of paper chromatography employing organic solvents (Report of the Chemistry Research Board 1947, H.M.S.O.; Arden, Burstall, Davies, Lewis, and Linstead, *Nature*, 1948, **162**, 691; Burstall, Davies, Linstead, and Wells, *ibid.*, 1949, **163**, 64; Linstead, *ibid.*, p. 598). Observations made in other laboratories have also recently been described (Lederer, *Nature*, 1948, **162**, 776; Pollard, McOmie, and Elbeih, *ibid.*, 1949, **163**, 292; Lederer, *ibid.*, p. 598; Lacourt, Sommereyns, Degeyndt, Baruh, and Gillard, *ibid.*, p. 999; Lederer, *Anal. Chim. Acta*, 1948, **3**, 476; *idem*, *Science*, 1949, **10**, 115; Osborne and Jewsbury, *Nature*, 1949, **164**, 443).

The following account provides a more detailed description of the qualitative separations carried out in this laboratory; quantitative separations will be the subject of a further paper. Methods of separating the metals constituting the ordinary qualitative analytical groups are described and the isolation of the constituents of mixtures containing some of the less common metals is also included. A few separations of anions have also been achieved. In some cases a particular separation has been extensively studied as to repeatability and interference

* Part I is regarded as the paper by Arden, Burstall, and Linstead (*J.*, 1949, S 311).

by various factors (see, *e.g.*, Part I, *loc. cit.*); in others the method is at a much earlier stage of development.

Paper chromatography has certain advantages over the conventional methods of qualitative inorganic chemical analysis—it is simple and reasonably rapid, costly special apparatus and chemicals are not necessary, and only small quantities of material are required for test purposes. Moreover, the method has proved successful for the separation and detection of groups of metals which are difficult to deal with by existing procedures, *e.g.*, the separation of the platinum metals from one another, of scandium from the rare earths and thorium, and of calcium, strontium, and barium from each other.

The technique is particularly useful in the separation and detection of groups of elements obtained by some suitable pretreatment of a complex mixture. The well-known analytical groups form a useful division of this kind; the further separation and detection of the elements in these groups can then be conveniently carried out by the methods now described.

It seems quite possible, also, that a complete system of qualitative chemical analysis could be developed on the basis of this new technique. The method is capable of giving good results in the hands of relatively inexperienced chemists. Separations, simple and easy to carry out, include Group IIa (Pb, Cu, Bi, Cd, and Hg), Group IIIb (Co, Ni, Mn, and Zn), the platinum metals and gold. More difficult separations are found in Group IIb (As, Sb, and Sn) and Group IV (Ca, Sr, and Ba). In routine operations such as are employed extensively in industry, the method should be particularly valuable since the conditions can be arranged to cover a particular series of metals or acid radicals and the procedure does not require continuous attention by a chemist.

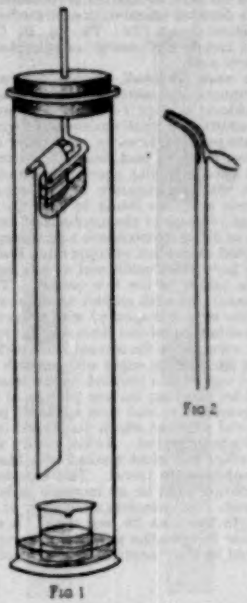

Fig. 1

Fig. 2

Fig. 3

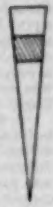

Fig. 4

Experimental.

Nearly all the experiments described in this paper were carried out on paper strips by a procedure which resembles, in general, that employed in similar organic work (Consden, Gordon, and Martin, *Biochem. J.*, 1944, **38**, 224). In view of the general interest of the method in the inorganic field, we give below a description of the technique which has been found most satisfactory over the past 4 years. The apparatus (Fig. 1) consists of a tall glass gas-jar closed with a tight fitting cork or a rubber bung which carries a glass rod to which is attached a glass boat. The boat is suspended about an inch below the bottom of the cork and serves as the container for the solvent employed in the separations. Two side arms are fused to the glass rod above the solvent container and these act as supports for a pair of paper strips, one strip being shown in position in the figure. In order to saturate the atmosphere in the cylinder with respect to the solvent, a layer of the latter is kept at the bottom of the cylinder. In some cases it is also necessary to control the amount of water vapour or acid in the atmosphere and for this purpose a beaker containing water, saturated salt solution, or aqueous acid saturated with solvent is placed on the bottom of the jar. It is advantageous also to maintain fairly constant temperature conditions, and in some cases the whole apparatus is kept in a thermostatically controlled (±1°) cabinet or bath.

The method of preparing the paper strip is substantially the same as in the earlier description (Arden, Burstall, Davies, Lewis, and Linstead, *loc. cit.*). A convenient volume (0·05 ml.) of the solution to be tested is placed near one end of a strip of filter-paper. This forms a wet patch about one inch square (Fig. 3) which is usually allowed to dry completely in air although in some cases the degree of drying is dependent on the chemical stability of the salts undergoing separation. In spite of the fact that the original solution is allowed to spread completely across the strip, little trouble has been experienced with edge effects. The strip is then hung vertically in the cylinder with the upper end immersed in the solvent contained in the glass boat. After the solvent has diffused down the paper a sufficient distance to effect a separation, the strip is removed from the cylinder, the solvent is allowed to evaporate, and the presence and position of the salts on the strip are determined by spraying with a suitable reagent. A simple type of atomiser suitable for this purpose is shown in Fig. 2. A large number of inorganic and organic reagents have been used. The criteria applied in choosing a developing reagent differ from those usually employed in selecting a spot-test reagent. It is not

necessary for the reagent to be specific for a certain radical, but it is desirable to have one which will give a delicate test for as many radicals as possible. Some of the reagents found particularly useful in this respect are diphenylthiocarbazone (dithizone), diphenylcarbazide, alizarin, rubeanic acid, salicylaldoxime, and morin. In many cases mixtures of two or more of these reagents are advantageous.

In order to obtain repeatable results it is necessary to be certain of constancy in composition of the solvents employed. In many cases, particularly with water-miscible solvents, small variations in the water content will alter considerably the efficiency of a separation. All the solvents used have received a suitable pretreatment which is described later.

The separations described below have been carried out on Whatman No. 1 or No. 3 filter-paper but a number of other papers have been used successfully. The length of the paper strip has varied from about 9 to 18 inches and, although usually this has been about 1 inch in width, it is useful in the detection of small quantities of material to employ a triangular strip as shown in Fig. 4, so that the extracted substance is concentrated in a smaller area of paper.

In the following description of various separations which have been made, a short note of the method recommended for each separation is recorded at the beginning of the appropriate section; this is then followed by a detailed consideration of the behaviour of the metals or acid radicals.

(a) *Analytical Group IIa*: Pb, Cu, Bi, Cd, *and* Hg. (With D. B. Rees Evans.) *Recommended method.* The metals are present as chlorides and the solvent used is *n*-butyl alcohol saturated with 3*N*-hydrochloric acid.

In earlier work (Burstall, Davies, Linstead, and Wells, *loc. cit.*) it was found that lead, copper, bismuth, cadmium, and mercury can be separated by the use of ethyl *iso*propyl ketone containing 10% (v/v) hydrochloric acid (*d* 1·18). These two liquids are not completely miscible, but one phase is obtained on addition of small amounts of *iso*propyl alcohol or larger amounts of methyl alcohol. Better separations are possible, however, with other solvents described below.

Separation of copper, lead, bismuth, cadmium, and mercury was achieved by using butyl alcohol or amyl alcohol saturated with aqueous hydrochloric acid as solvent. The degree of separation obtained depended on the concentration of the aqueous acid used (Fig. 5). Butyl alcohol saturated with 3*N*-hydrochloric acid was found to give the most efficient separation. It was prepared by shaking together equal volumes of the alcohol and 3*N*-hydrochloric acid, the top layer being used. A solution of the metals in dilute hydrochloric acid was spotted on a strip of paper which had to be at least 18" long to obtain a good separation of copper and lead. The spot was allowed to dry in air for one hour. Use of a wet spot gave wider bands and a more rapid movement of solvent down the strip but did not much affect the R_F values of the five metals. The solvent was allowed to flow for 15—18 hours in an atmosphere saturated with respect to both organic solvent and aqueous phases. After evaporation of the solvent, the strip was sprayed with a solution of dithizone in chloroform. Mercury was detected as a pink band behind the solvent front and was followed by cadmium as a purple band. Although cadmium and mercury were not in the solvent front and each metal was separated from the other, both bands had sharp leading and trailing edges with a width less than that of the original spot. Bismuth appeared as a purple, and copper as a purplish-brown band. Lead, which gives only a weak colour with dithizone, was detected by spraying the top portion of the strip with an aqueous solution of rhodizonic acid; a bright blue band due to lead then appeared just below the copper.

A number of different effects was noted on varying the concentration of the acid with which the butyl alcohol was saturated. As the acidity was decreased, (*a*) the bands of all five metals became more diffuse (this effect was most marked with bismuth), (*b*) the R_F value of each cation decreased but to a different extent for each metal. This resulted in a better separation of cadmium and mercury which was partly counteracted by an increase in band width and a decrease in the degree of separation of copper and lead. No complete separation of copper and lead was achieved, even after 18 hours, when acid of strength less than 3*N*. was used. A series of R_F values obtained by using different acidities is shown in Table I. For the purpose of these measurements an R_F value is taken as the ratio of the distance moved by the " centre of gravity " of a band to the distance moved by the solvent.

TABLE I.

Variations in R_F values with change in acid concentrations.

Solvent.	Cu.	Pb.	Bi.	Cd.	Wet solvent front.	Hg.
Satd. with H_2O	0·04, 0·04	0·05, 0·05	0·50, 0·49	0·60, 0·62	0·65, 0·66	0·73, 0·74
Satd. with 1*N*-HCl ...	0·08, 0·08	0·12, 0·11	0·55, 0·52	0·66, 0·63	0·70, 0·68	0·76, 0·78
Satd. with 2*N*-HCl ...	0·13, 0·11	0·17, 0·12	0·57, 0·54	0·69, 0·66	0·72, 0·69	0·76, 0·76
Satd. with 3*N*-HCl ...	0·20, 0·20	0·27, 0·27	0·60, 0·58	0·77, 0·77	0·79, 0·79	0·81, 0·81

Two solvent phases exist on the paper strip, an upper area in which the paper is saturated with water and below that a region of dry solvent. When the solvent contained both hydrochloric acid and water the upper wet phase was strongly acid, but the lower dry phase was almost free from acid. The boundary between these two phases was not easily detected until the strip was sprayed with a suitable reagent, but on spraying the strip with dithizone or diphenylcarbazide solution a band of what appeared to be cadmium was found just in front of the main cadmium band. A similar band was obtained when a blank strip of paper was used and did in fact mark the position of the wet solvent boundary. The material causing the colour has not been identified but appears to be organic rather than inorganic since it gives a negative test for metals such as copper and iron normally found in cellulose. The position of the wet solvent front was also found by taking advantage of the difference in acidity of the two phases and spraying the strip with a suitable indicator. The R_F value of the wet solvent front was measured in a number of cases and is recorded in Table I.

As the concentration of aqueous acid used was increased above 3*N*-hydrochloric acid the bismuth and

FIG. 5.

Group IIa.

Solvent: Butyl alcohol saturated with

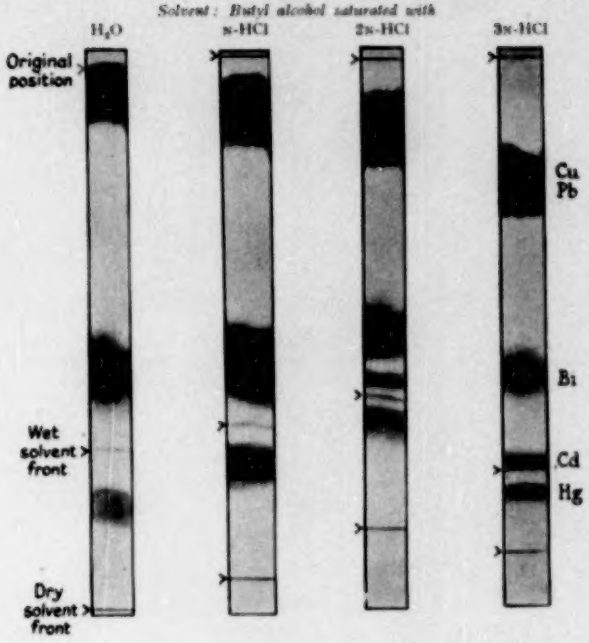

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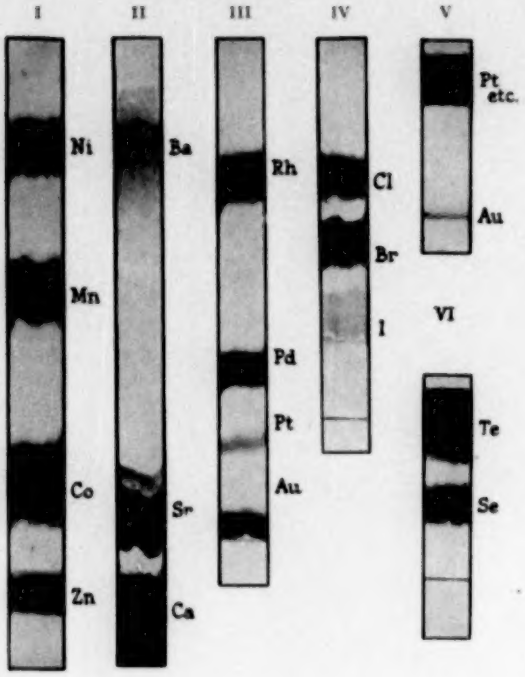
Fig. 6.



lead bands were displaced backwards towards the copper whereas the cadmium band moved forward towards the mercury. The use of butyl alcohol containing 10% (v/v) of hydrochloric acid (*d* 1·18) resulted in mercury and cadmium being found in a mixed band. Copper and bismuth also formed a mixed band but lead was now in a separate band behind the copper. In order to get repeatable figures for R_F values it was essential that the atmosphere be completely saturated with respect to butyl alcohol and aqueous acid phases. Well-separated bands of bismuth, cadmium, and mercury were often obtained when at the beginning of a run the atmosphere was incompletely saturated, but results were not accurately repeatable. As an aid to maintaining a constant atmosphere the temperature was controlled at 22°. The R_F values appeared to be fairly independent of the concentration of each of the metals, of the total concentration of metals, and of the acid concentration of the original solution. Bismuth was more affected by such factors than the other metals. A difference in R_F values was noted in tests with varying times of solvent diffusion. Table II gives R_F values obtained with butyl alcohol saturated with aqueous acid of different strengths. The effect of time of running is noticeable in each case but agreement between duplicate strips is good. Unless otherwise stated, the amount of copper, bismuth, cadmium, and mercury was 100 μg. of each metal, and 40 μg. of lead were used.

TABLE II.

R_F *Values using butyl alcohol* + 3*N*-HCl.

	Time of run.							
Metal.	7 hrs.		8 hrs.		15 hrs.		16 hrs.	
Cu	0·10		0·21	0·21	0·24	0·25	0·23	0·25
Pb	0·24		—	—	0·30	0·30	—	—
Bi	0·56		0·58	0·60	0·69	0·70	0·74	0·73
Cd	0·71		0·69	0·70	0·87	0·89	0·89	0·88
Hg	0·80		0·73 *	0·75 *	0·91	0·92	0·92 *	0·92 *

* Only 10 μg. of Hg present.

R_F *Values using butyl alcohol* + 2·5*N*-HCl.

	Time of run.							
Metal.	5 hrs.		8 hrs.		16 hrs.		16 hrs.	
Cu	0·15	0·17	0·15	0·16	0·18	0·19	0·19	0·19
Bi	0·55	0·54	0·58	0·55	0·63	0·63	0·62	0·62
Cd	0·66	0·66	0·67	0·65	0·73	0·73	0·73	0·72
Hg	0·73	0·72	0·77	0·75	0·79	0·78	0·78	0·76

R_F *Values using butyl alcohol* + 2*N*-HCl.

	Time of run.							
Metal.	5 hrs.		8 hrs.		16 hrs.		16 hrs.	
Cu	0·15	0·13	0·13	0·13	0·16	0·15	0·14	0·14
Bi	0·53	0·52	0·54	0·54	0·60	0·58	0·58	0·58
Cd	0·62	0·61	0·64	0·62	0·70	0·68	0·67	0·64
Hg	0·70	0·71	0·73	0·74	0·75	0·75	0·74	0·72

TABLE III.

R_F *Values with different solvents prepared with* 2·5*N*-HCl.

Metal.	Method (*a*).		Method (*b*).		Method (*c*).	
Cu	0·17	0·18	0·19	0·20	0·16	0·15
Pb	0·25	0·25	0·27	0·27	0·20	0·20
Bi	0·59	0·63	0·63	0·65	0·64	0·62
Cd	0·68	0·73	0·75	0·76	0·75	0·73
Hg	0·74	0·80	0·79	0·80	0·81	0·79

The term "butyl alcohol saturated with hydrochloric acid" is capable of several interpretations, but from the R_F values given in Table III it will be seen that no significant difference is made to the separation when three different methods are used for saturating the solvent: (*a*) by shaking together equal volumes of acid and butyl alcohol, (*b*) by shaking two volumes of acid and one of butyl alcohol, (*c*) by adding acid to butyl alcohol until two phases just do not separate.

A similar pattern in the results was obtained by using amyl alcohol in place of butyl alcohol. The optimum concentration of aqueous hydrochloric acid used for saturating the alcohol was again 3*N*. A similar two-phase effect was observed, as was found with butyl alcohol. One marked difference obtained with amyl alcohol was an absence of separation between copper and lead. A large number of variations in the solvent mixture was tried in order to achieve a separation but without success.

As the acid concentration was increased beyond 3*N*., the same closing up of the bands (already described for butyl alcohol) was observed. If the hydrochloric acid concentration was raised until the amyl alcohol contained 20% (v/v) of hydrochloric acid (*d* 1·18), lead was obtained as a separate band above the copper. The R_F values obtained on using amyl alcohol which had been shaken with an

equal volume of 2N-hydrochloric acid are given in Table IV. Temperature was again controlled at 22° and time of running was 18 hours.

TABLE IV.

R_F Values using amyl alcohol + 2N-hydrochloric acid.

Metal.	Cu.	Bi.	Cd.	Hg.
R_F value	0·07, 0·07	0·36, 0·36	0·63, 0·64	0·70, 0·72

Copper, bismuth, cadmium, and mercury have been separated from lead by using methyl alcohol containing 5% (v/v) of concentrated hydrochloric acid as solvent. The solution of the metals in dilute hydrochloric acid was spotted on a strip and allowed to dry thoroughly in air. The copper, bismuth, cadmium, and mercury travel in mixed diffuse bands with mercury in the solvent front, while the lead moves much more slowly. A lower concentration of hydrochloric acid in the solvent results in a diffuse lead band, whereas higher concentrations cause the lead to move sufficiently fast to overlap the copper.

Another separation of Group IIa metals has been achieved by using pyridine. Bismuth, copper, cadmium, and mercury have been separated in that order. Lead and bismuth remained in the original spot while mercury was just in front of, but overlapping, the cadmium. The original solution of the metals in dilute hydrochloric acid was spotted on a paper strip and then made alkaline by exposure to ammonia vapour. A better separation was achieved by this method than by leaving the original spot acid.

(b) *Analytical Group IIb* : As, Sb, *and* Sn. (With N. F. KEMBER.)—*Recommended method.* The metals are present as their lower chlorides and the solvent consists of a mixture of acetylacetone saturated with water, with 0·5% (v/v) of hydrochloric acid (*d* 1·18) and 25% (v/v) of acetone.

A very large number of solvents have been examined for the separation of arsenious, antimonous, and stannous chlorides. Many solvents gave a clear-cut separation of antimony and tin from arsenic, but few have been found capable of completely separating antimony and tin. Development with gaseous hydrogen sulphide was used in early tests as a means of detecting the arsenic, antimony, and tin bands; it then appeared possible to separate antimony and tin with a number of solvents. The use of a chloroform solution of dithizone, which was a more sensitive spot test, showed that, while most of the tin appeared to be in a concentrated band separated from antimony, a small amount of tin tailed back to the front edge of the antimony. The separation of arsenic, antimony and tin using ethyl acetate (Burstall, Davies, Linstead, and Wells, *loc. cit.*) suffers from the same disadvantage. The best conditions for obtaining repeatable results with ethyl acetate were as follows. The original solution of the metals in dilute hydrochloric acid was spotted on to a paper strip and allowed to dry in air for 1 hour. The strip was then tested as already described with ethyl acetate saturated with water in an atmosphere of ethyl acetate and water vapour. After evaporation of the solvent the strip was sprayed with a solution of dithizone in chloroform. The arsenic was detected as a very sharp, narrow, yellow band, while the antimony was lower down the strip in a wider reddish band with sharp front and rear edges, and the tin formed a purple band, with a sharp front edge and a trailing rear edge well behind the solvent front. Similar results were obtained with methyl acetate and methyl propyl ketone. Various modifications were tried in order to obtain a better tin band, *e.g.*, (*a*) addition of ethyl acetoacetate to ethyl acetate, (*b*) the use of methyl acetate in an atmosphere of chloroform vapour, (*c*) addition of chloroform to methyl acetate, (*d*) addition of various concentrations of hydrochloric acid and water to : methyl propyl ketone ; methyl propyl ketone–acetone mixtures ; methyl acetate–acetone mixtures, etc. A good separation of all three metals was sometimes obtained, but results with respect to the tailing of the tin band were difficult to repeat. Of the alcohols tried, butyl alcohol saturated with water gave the best separations. Antimony and tin were well separated from arsenic, which formed a more diffuse band than that obtained with esters or ketones. Both antimony and tin furnished very narrow bands which, in an atmosphere saturated with the solvent, were very close together or just touching. Addition of hydrochloric acid to the alcohol resulted in overlapping of the antimony and tin bands. Good bands were obtained for all three metals on using ethyl ether saturated with water, but again the antimony and tin bands touched. Other solvents examined include : acetone, methyl ethyl ketone, *cyclo*hexanone, isopropyl ether, " Cellosolve " and its derivatives, pyridine, 2 : 2′-dichlorodiethyl ether, methyl isobutyl ketone, dioxan, formic acid, acetic acid, triacetin, and ethylene dichloride.

Acetylacetone gave the best separation of tin and antimony so far achieved. Separations were first obtained by using acetylacetone saturated with water. There was a tendency, also found with other solvents, for a small amount of tin to remain behind in the original spot. To prevent this effect 0·5% (v/v) of hydrochloric acid (*d* 1·18) was added to the solvent together with 25% (v/v) of acetone. The acetone was added in amount sufficient to enable the hydrochloric acid and acetylacetone to form a clear solution. The acetylacetone was freshly distilled, and the fraction of b. p. 137—141° was collected. This fraction was saturated with water, and to 7·5 ml. of the saturated solvent were added 0·05 ml. of concentrated hydrochloric acid and 2·5 ml. of dry acetone. A solution of arsenious, antimonous, and stannous chlorides in dilute hydrochloric acid (2—4N.) was spotted on a paper strip and allowed to dry in air for 15 minutes. The experiment was then run with this solvent for one hour (solvent movement 15 cm.) in an atmosphere saturated with respect to a saturated solution of acetylacetone in water. The complexes formed with acetylacetone were extremely stable, particularly the one formed with tin. Accordingly, the following method was used to develop the bands : the strip was removed from the extraction vessel, and the solvent allowed to evaporate for several minutes. Before the strip was completely dry it was sprayed with a chloroform solution of dithizone and then allowed to dry thoroughly. The tin was found in the solvent front and had a diffuse trailing edge. The antimony formed a wider band with a sharp front and slightly diffuse rear edge ; approximate R_F value 0·5. The arsenic was present in a very narrow band ; R_F value approx. 0·2.

(c) *Analytical Group IIIa* : Fe, Al, *and* Cr.—*Recommended method.* The metals are present as chlorides and the solvent used is glacial acetic acid containing 25% (v/v) of dry methyl alcohol.

Although the separation of iron from aluminium and chromium can be carried out easily with a large number of solvents, the separation of aluminium from chromium was more difficult. A convenient solvent for the separation of iron as ferric chloride from aluminium and chromic chlorides was acetone containing hydrochloric acid. The acid concentration was not critical but acetone +10% (v/v) of hydrochloric acid (*d* 1·18) produced a narrow band of iron in the solvent front with little movement of aluminium and chromium. Increase in the acid or water content of the acetone resulted in increased movement of aluminium and chromium but always in overlapping bands. A large number of solvents were tested for the separation of aluminium and chromium including: methyl, ethyl, isopropyl, butyl, and amyl alcohols, methyl propyl ketone, ether, isopropyl ether, "Cellosolve," "Carbitol," ethyl acetate, and pyridine. These solvents were tested with varying concentrations of water and hydrochloric acid and in mixtures of these liquids. Separation of aluminium and chromium was not obtained although movement of both metals often took place. In all these experiments the original solution consisted of a solution of ferric, aluminium, and chromic chlorides in dilute hydrochloric acid. Chromium as chromate or dichromate was extremely soluble in organic solvents but reduction to chromic chloride occurred, resulting in a diffuse band of chromium stretching from the solvent front to the original spot.

Aluminium as the trichloride was extracted in the solvent front by aqueous acetic or formic acid solutions (Lacourt *et al.*, *loc. cit.*). With glacial acetic acid, aluminium and chromium moved slightly and together, and iron was extracted in a band some way behind the solvent front. As the concentration of water in the solvent was increased, so did the rate of movement of the three metals, the movement of aluminium being much greater than that of chromium and iron. If a mixture of equal volumes of glacial acetic acid and water was used as solvent, aluminium was found in the solvent front, with iron in a separate band just behind the aluminium, and chromium still further behind, but only just separated from iron. By adjusting the water concentration it was possible to obtain a separation of chromium, aluminium, and iron in that order, proceeding down the strip. Such a separation was achieved by the use of acetic acid containing 10% (v/v) of water but the bands were all very diffuse.

The same type of variation in movements obtained with acetic acid–water mixtures was also obtained with acetic acid–methanol and acetic acid–ethanol mixtures. With these mixtures better bands were obtained and there was less tendency for the formation of the double bands of chromium and iron often obtained with aqueous acetic acid. The best separations were obtained with glacial acetic acid containing 25% (v/v) of dry methyl alcohol. The test solution of iron, aluminium, and chromium chlorides was prepared in 5*N*-hydrochloric acid, spotted on to a paper strip, and allowed to evaporate to dryness in air. Use of a solution containing insufficient free hydrochloric acid gave incomplete extraction and double-band formation of iron. The experiment was allowed to run for 12 hours in an atmosphere saturated with respect to the mixed solvents. A further improvement in the separation was obtained by maintaining a low humidity in the extraction chamber, *e.g.*, by keeping a saturated solution of potassium carbonate in the bottom of the vessel. In order to detect the position of the bands, the solvent was allowed to evaporate and the strip was cut lengthwise into two portions. One portion was sprayed with an alcoholic solution of alizarin, made alkaline by exposure to ammonia vapour, and then warmed. Aluminium appeared as a red band well separated from a purple band due to iron, which was some way behind the solvent front. The other portion of the strip was sprayed first with aqueous sodium peroxide solution and then with a solution of benzidine in acetic acid. Chromium was indicated as a bright blue band just behind the aluminium.

Unsuccessful attempts at separation were made when the nitrates of iron, aluminium, and chromium were used with solvents containing nitric acid or potassium thiocyanate.

(d) *Analytical Group IIIb*: Ni, Mn, Co, *and* Zn. (With Miss J. N. Clarke.)—*Recommended method.* The metals are present as chlorides, and the solvent used is acetone containg 5% (v/v) of water and 8% (v/v) of hydrochloric acid (*d* 1·18).

To obtain a separation of nickel, manganese, cobalt, and zinc (Fig. 6; Strip I) a solution of the metals in dilute hydrochloric acid was spotted on to a paper strip and allowed to dry in air. The solvent consisted of acetone containing 5% (v/v) of water to which was added 8% (v/v) of hydrochloric acid (*d* 1·18). A solvent movement of about 25 cm. was allowed in an atmosphere saturated with respect to the solvent. The solvent was allowed to evaporate and the strip exposed to ammonia vapour and then sprayed with a mixture of alizarin, rubeanic acid, and salicylaldoxime in alcohol. Nickel was detected as a blue band which had just moved from the original spot. Manganese formed a brownish band below the nickel, whereas cobalt formed a brown band below manganese and zinc was in the solvent front. Approximate R_F values were: Ni, 0·07, Mn 0·3, Co 0·6, Zn 0·9.

The separation of nickel, manganese, cobalt, copper, and iron by using a mixture of methyl propyl ketone, acetone, and hydrochloric acid has been reported by Arden *et al.* (*loc. cit.*), and the application of this separation to the quantitative estimation of these metals will be described in another paper.

(e) *Analytical Group IV*: Ca, Sr, *and* Ba.—*Recommended method.* The metals are present as chlorides, and the solvent used is pyridine containing 20% (v/v) of water and 1% (w/v) of potassium thiocyanate.

This mixture of metals has not proved easy to separate. The use of solvents alone or containing water or acid was not effective with the chlorides or nitrates. With potassium thiocyanate in certain solvents some success was achieved, and of these solvents pyridine containing 10—30% of water (and 0·5—1·0% of thiocyanate) proved the best. An aqueous solution of the alkaline-earth metals as chlorides was spotted on the paper strip and allowed to dry in air. Extraction was allowed to proceed for 5—6 hours which gave a run of about 20 cm. The atmosphere in the cylinder was saturated with respect to pyridine, and the relative humidity was also controlled between 65 and 80% by having at the bottom of the cylinder a beaker containing either saturated ammonium nitrate or ammonium chloride solution. After the paper had been dried, the separated salts were developed with alizarin to identify the calcium and with sodium rhodizonate to reveal barium and strontium. The calcium occurred just behind the solvent front, with the strontium a little way above the calcium (Fig. 6; Strip II). Under the best conditions the movement of barium is slight, but in some cases, particularly on warmer days if the temperature is not controlled, there is a tendency for the barium to move downwards towards the

strontium. This movement is often irregular and appears to be connected with the movement of the strontium, for it decreases or stops once the calcium and strontium are separated from the barium.

(f) *Analytical Group V*: Li, Na, *and* K. *Recommended method.* The metals are present as their chlorides in neutral solution and the solvent used is methyl alcohol.

Only preliminary work has been carried out on the separation of the alkali metals and so far only lithium, sodium, and potassium have been examined. With an aqueous solution containing 100 μg. of each of the metals as chlorides, in 0·05 ml. of solution, separations were obtained with methyl alcohol as solvent. The position of the alkali-metal bands was found by spraying with a mixed solution of silver nitrate and fluorescein and then drying the strip. Three chloride bands were detected, lithium some distance behind the solvent front, sodium about half-way between the original position and the solvent front, and the potassium band just below the original position.

(g) *The Platinum Metals*: Pt, Pd, Rh, Ir, Ru, Os, *and* Au.—*Recommended method.* The metals are present as their chlorides or sodium chloro-salts and the solvent used is methyl ethyl ketone containing 30% (v/v) of hydrochloric acid (*d* 1·18).

Several methods of separation of the platinum metals have been achieved depending on the solvent used and on the valency states of the metals in solution. In order to maintain standard conditions, a chloride solution was prepared by fusing gold, palladium, platinum, rhodium, and iridium chlorides with sodium peroxide. A second mixture also included ruthenium and osmium. The melt was dissolved in water and acidified with hydrochloric acid. The chloride solution was spotted on a paper strip and allowed to dry thoroughly in air. For the subsequent detection of the metals, stannous chloride was found to be a suitable developing reagent for platinum, palladium, gold, and rhodium. A more sensitive reagent was a mixture of stannous chloride and potassium iodide solutions. The strip was warmed gently for the full development of the rhodium colour. Iridium was reduced to the colourless trichloride by stannous chloride. A good spot test was not found for iridium, but reoxidation to the brown tetrachloride was found to be fairly satisfactory. A solution of thiourea in 5*N*-hydrochloric acid was used to test for ruthenium and osmium, and the strip was warmed to develop the colours fully. The work has been mainly directed to the separation of gold, platinum, palladium, iridium, and rhodium and only a small number of experiments have included ruthenium and osmium. A number of solvents separated gold, platinum, iridium, and osmium from rhodium provided that the rhodium was present as sodium chlororhodite (Na_3RhCl_6); rhodium chloride ($RhCl_3$) is soluble in a number of organic solvents. Acetone +5% of hydrochloric acid (*d* 1·18) has been found particularly satisfactory provided that the ketone is dry and freshly distilled. The rhodium was left in the original spot, and gold, platinum, palladium, iridium, and osmium were obtained in overlapping bands, gold being in the solvent front. If, in the absence of gold, the original solution was reduced with sulphur dioxide, platinum, palladium, and osmium were still extracted from rhodium with acetone +5% (v/v) of hydrochloric acid (*d* 1·18) but iridium and ruthenium then remained with the rhodium.

Iridium tetrachloride moved together with the platinum band with all the solvents investigated, but in the presence of an organic solvent containing hydrochloric acid the tetrachloride was reduced or partly reduced to the trichloride. Iridium trichloride behaved similarly to sodium chlororhodite. This reduction of Ir^{IV} to Ir^{III} increased as the concentration of hydrochloric acid in the organic solvent increased. With acetone containing 5% (v/v) of hydrochloric acid (*d* 1·18) the extraction of iridium tetrachloride from rhodium was practically complete with little or no reduction to the trichloride. The presence of an oxidising agent such as sodium chlorate further aided the extraction by preventing reduction. Ruthenium was extracted by acetone +5% (v/v) of hydrochloric acid (*d* 1·18) as a wide diffuse band stretching from solvent front to original spot. If sulphur dioxide was first passed through the ruthenium chloride solution, the resulting solution was not extracted by the acetone solvent but remained with rhodium and tervalent iridium. The reduction of the chloride solution of the mixed platinum metals with sulphur dioxide first gave a clear solution, but in a short time a precipitate was formed. This deposit was shown to be due to insoluble ruthenium and osmium compounds. The reduced solution of platinum, palladium, and iridium chlorides was stable.

The separation of rhodium, iridium, platinum, palladium, and gold into four bands, one of which contained both rhodium and iridium, using methyl propyl ketone +30% (v/v) of hydrochloric acid (*d* 1·18) has already been reported (Burstall *et al.*, *loc. cit.*). The separation of silver, copper, palladium, platinum, and gold by using butyl alcohol saturated with 8-hydrochloric acid has also been recorded by Lederer (*Nature*, 1948, **162**, 776). Methyl ethyl ketone containing 30% (v/v) of hydrochloric acid (*d* 1·18) has been used in place of methyl propyl ketone with satisfactory results (Fig. 6; Strip III). Either of the ketonic solvents rapidly reduced Ir^{IV} to the comparatively immobile Ir^{III} which moved with rhodium. With less than 30% (v/v) of hydrochloric acid (*d* 1·18) in methyl ethyl ketone, Ir^{IV} was partly extracted from the rhodium band owing to incomplete reduction. With methyl propyl ketone containing less than 30% (v/v) of hydrochloric acid (*d* 1·18) double bands of platinum were formed. On addition of ruthenium and osmium to the system, ruthenium was found with the rhodium and iridium, while osmium was found between, but not completely separated from, the gold and the platinum. The behaviour of ruthenium and osmium was similar with both ketonic solvents.

A number of R_F values were measured and shown to be fairly constant (Table V) providing conditions were sufficiently standardised. The solvent was prepared by dissolving 30 ml. of concentrated "AnalaR" hydrochloric acid (*d* 1·18) in 70 ml. of methyl propyl ketone or methyl ethyl ketone and the atmosphere of the separation vessel was saturated with respect to the solvent. The solution of platinum metals in 2*N*-hydrochloric acid was spotted on a paper strip and dried for 1 hour.

The solvent was freshly made up each day, since, when kept for a long time with acid, both ketones undergo some decomposition and darkening. The normality of the concentrated hydrochloric acid is likely to vary, but this will not affect the separation although some alteration in R_F values will be observed.

For the separation of rhodium and iridium after removal of gold, platinum, and palladium with either ketonic solvent, the test was run first with methyl propyl ketone or methyl ethyl ketone +30% (v/v) of hydrochloric acid (*d* 1·18), the solvent was allowed to evaporate, and the strip then sprayed with

an oxidising agent, *e.g.*, chlorine water. After drying, the strip was re-run with acetone containing 5% (v/v) of hydrochloric acid (*d* 1·18). This second extraction removed the iridium in the new solvent front, which was then allowed to move to a point between the rhodium and palladium bands.

A number of other solvents have been found to give successful or partly successful separations. "Carbitol" or "Cellosolve" containing 20% (v/v) of hydrochloric acid (*d* 1·18) gave a separation of gold, platinum, palladium, and rhodium into 4 bands; "Cellosolve acetate" containing hydrochloric acid (*d* 1·18) gave similar results, but in all three cases quadrivalent iridium was found with the palladium band.

A graduated series of results was obtained on using the alcohols with 20% (v/v) of hydrochloric acid (*d* 1·18). These mixtures being used, the separation improved on ascending the series, methyl, ethyl, butyl, amyl. With amyl alcohol, separation of gold, platinum, palladium, and rhodium into four bands was obtained, but the platinum and palladium bands remained in contact. Iridium was reduced by the amyl alcohol solvent as already described for the ketonic solvents. With butyl alcohol saturated with 2*N*-hydrochloric acid a good separation of rhodium, platinum, palladium, and gold was obtained but iridium was found in a disperse band stretching from the gold to palladium.

(h) *Separation of Gold from the Platinum Metals.—Recommended method.* The metals are present as their chlorides, and the solvent used is ethyl ether containing 2% (w/v) of dry hydrogen chloride and 7·5% (v/v) of dry methyl alcohol.

TABLE V.

R_F Values of platinum metals.

Operator.	Solvent.	Time of run, hrs.	R_F Values. Au.	Os.	Pt.	Pd.	Rh and Ir.	Ru.	Wt. of each metal present, μg.
A	COMeEt + 30% HCl	16	0·91	—	0·76	0·56	0·06	—	50
,,	,,	16	0·91	—	0·78	0·56	0·05	—	25
,,	,,	8	0·95	0·92	0·84	0·61	0·09	0·09	50
,,	,,	8	0·97	0·93	0·84	0·60	0·09	0·08	25
B	,,	16	0·95	—	0·84	0·64	0·17	—	50
,,	,,	16	0·97	—	0·85	0·65	0·17	—	25
,,	,,	8	0·97	—	0·83	0·65	0·16	—	50
,,	,,	8	0·97	—	0·82	0·62	0·15	—	25
A	COMePr + 30% HCl	16	0·91	—	0·75	0·53	0·11	—	50
,,	,,	16	0·92	—	0·75	0·52	0·10	—	25
,,	,,	8	0·96	0·89	0·81	0·56	0·11	0·07	50
,,	,,	8	0·96	0·91	0·81	0·56	0·11	0·07	25
B	,,	8	0·98	—	0·80	0·57	0·17	—	50
,,	,,	8	0·98	—	0·80	0·57	0·15	—	25

A useful quick method for the detection of small amounts of gold in chloride solutions of the platinum metals has been discovered. The solvent consisted of ethyl ether containing 1—2% (w/v) of dry hydrogen chloride to which was added 7·5% (v/v) of dry methyl alcohol. This mixture extracted gold in a narrow band in the solvent front, while the platinum metals remained in the original spot (Fig. 6; Strip V). By using this solvent it was found possible to detect 1 μg. of gold in several hundred times the amount of each of the platinum metals.

Several practical difficulties have been observed. In experiments with pure gold chloride solution, it was found that when an aqueous solution was allowed to evaporate to dryness on filter-paper, some of the gold salt was reduced to the metal and was not subsequently extracted. A solution in fairly concentrated (>2*N*.) hydrochloric acid, however, could be evaporated to dryness on a paper strip without reduction to the metal and subsequent extraction was complete. With a 12-hour gap between the drying and running of a strip, partial reduction to gold occurred even with use of concentrated hydrochloric acid. In all work with solutions containing gold chloride, therefore, the original solution was made acid with hydrochloric acid and after being spotted on a paper strip was allowed to dry in air for 1 hour and then run with solvent. The methyl alcohol was added to the solvent in order to increase the efficiency of extraction, by decreasing the rate of movement of ether which was too fast for complete extraction of the gold chloride. Addition of too much methyl alcohol brought about partial reduction of the auric chloride. Increase in the concentration of dry hydrogen chloride in the solvent to 4% (w/v) also caused reduction, but variation in the concentration between 1 and 2% (w/v) was without effect. The test was run in an atmosphere of solvent vapour, but the extreme volatility of the solvent made constant atmospheric conditions difficult to maintain. A number of modifications and different solvents were tried in order to overcome this disadvantage, but either the platinum metals moved or the gold was extracted in a band which tailed badly. An example of a solvent which produced tailing was glacial acetic acid containing 4% (v/v) of hydrochloric acid.

(i) *Separation of Mercury from other Metals.* (With Miss M. N. JENKINS.)—*Recommended method.* The metals are present as their chlorides and the solvent used is methyl acetate containing 3% (v/v) of methyl alcohol and 10% (v/v) of water.

The separation of mercury by using tetrahydrosylvan as solvent has already been reported (Arden *et al.*, *loc. cit.*). Methyl acetate was found to be a suitable and more readily available solvent for the extraction of mercury as chloride from the following metals: lead, copper, bismuth, cadmium, arsenic, antimony, iron, aluminium, chromium, nickel, cobalt, manganese, and zinc. A number of other solvents including ethyl acetate and methyl propyl ketone also gave good results. Mercuric chloride is

soluble in a large number of organic solvents but is exceptional in that the partition coefficient between most solvents and water falls off rapidly as the acidity of the aqueous layer is increased. Methyl acetate extracts mercuric chloride under widely differing conditions but the width of the mercury band and its position relative to the solvent front vary considerably with small changes. Mercury was extracted in a very narrow band in the solvent front by the following method.

The test solution, which should not contain more than 5% (v/v) of hydrochloric acid (*d* 1·18) and must have pH <2, was spotted on a paper strip and allowed to evaporate for 10—15 minutes. The solvent was methyl acetate with 10% (v/v) of water and 3% (v/v) of methyl alcohol or the constant-boiling mixture of methyl acetate and methyl alcohol with an added 7% (v/v) of water. The solvent was run in an atmosphere saturated with respect to the vapour of a saturated solution of methyl acetate in water and the temperature was kept constant at 22°. The solvent moved sufficiently far in 20—30 minutes to effect a complete separation. After the solvent had been allowed to evaporate, the strip was made alkaline by exposure to ammonia vapour and sprayed with an alcoholic solution of diphenylcarbazide; mercury was then indicated by a blue band in the solvent front. Two solvent phases were clearly distinguishable on the strip; an upper aqueous phase containing impurities, and a dry solvent phase with the mercury in the front edge. The extent to which water could usefully be added to the solvent was controlled by the behaviour of the upper wet phase. As the amount of water in the solvent was increased the extraction of mercury was improved, but if the amount of water added was increased beyond a definite limit, which varied with temperature, only one aqueous phase was obtained on the strip and all the metals present moved down to the solvent front. The amount of water permissible decreased with increase in temperature. The original spot was not allowed to dry over a prolonged period in order to avoid the formation of basic salt which retained the mercury. It was possible to detect with ease 1 μg. of mercury by this method in the presence of a large excess of other metals. Some interference in the extraction of mercury was noted with concentrations of copper in the test solution exceeding 10% (w/v) but the extraction was largely independent of the ratio of mercury to copper.

(j) *Separation of Selenium and Tellurium.* (With N. F. Kember.)—*Recommended method.* The metals are present in dilute nitric acid solution, and the solvent used is dry butyl alcohol containing 40% (v/v) of dry methyl alcohol.

The following method has been developed for the separation of selenium and tellurium. A solution of the elements as selenite and tellurite in dilute nitric acid was spotted on a paper strip and allowed to dry thoroughly in air. The strip was treated with a solvent consisting of a mixture of 60% (v/v) of dry butyl alcohol and 40% (v/v) of dry methyl alcohol, in an atmosphere saturated with respect to the solvent vapour and with a relative humidity maintained at 50%. The solvent was allowed to diffuse 8—10 cm. down the strip (approx. 2 hours). After evaporation of the solvent, the strip was developed by spraying with stannous chloride solution. The tellurium which had moved only slightly from the position of the test sample was indicated as a black band, whereas selenium formed an orange band half-way between the solvent front and the original spot position (Fig. 6; Strip VI). The lower limit of detection for selenium, with the normal 1" wide strip and stannous chloride as developer, was 5 μg., but 1 μg. was detected in 1000 μg. of tellurium by using a triangular strip. This separation was also obtained with test solutions consisting of tellurate and selenate in dilute nitric acid, but more difficulty was experienced in detecting the position of the bands. Sulphate, if present, did not affect the separation but remained with the tellurium. The original spot on the paper strip had to be thoroughly dry, otherwise excessive tailing of tellurium occurred; moveover, both alcohols in the solvent mixture must be dry. Increase in the percentage of methyl alcohol in the solvent mixture gave more rapid extraction of selenium in a narrower band but excessive forward tailing of tellurium was also obtained. The humidity of the extraction vessel was controlled at approximately 50% by means of a saturated solution of calcium nitrate kept in the bottom of the container. Variation in the humidity was found to alter the extraction in the following ways: (*a*) Increase in humidity gave more complete extraction of selenium. (*b*) At relative humidities >30%, slight movement of tellurium took place; this increased as the humidity was raised. (*c*) The relative movement of selenium decreased as the humidity was increased. (*d*) "Edge effects" for selenium decreased as the humidity was raised.

The conditions chosen for extraction therefore represent a compromise.

(k) *Separation of Thorium, Scandium, and the Rare Earths.* (With N. F. Kember.)—*Recommended method.* The metals are present as nitrates, and the solvent used is tetrahydrosylvan containing 5% (v/v) of water and 10% (v/v) of nitric acid (*d* 1·42).

The separation of scandium from the rare earths on a column of cellulose by aid of an ethyl ether–nitric acid mixture has already been briefly reported (Burstall *et al.*, *loc. cit.*). A solvent containing diethyl ether is not suitable for use with the paper-strip technique, but tetrahydrosylvan was found to be a suitable solvent, after addition of water and nitric acid, for the separation of scandium and thorium from each other and from the rare earths, on the same strip.

A solution of the rare earths, thorium, and scandium in dilute nitric acid was spotted on a paper strip and dried thoroughly in air. The solvent, consisting of tetrahydrosylvan containing 5% (v/v) of water and 10% (v/v) of nitric acid (*d* 1·42), was allowed to diffuse about 15 cm. down the paper strip. By controlling the relative humidity of the atmosphere at about 80% with a saturated solution of ammonium chloride in the bottom of the extraction vessel, a narrow and concentrated band of scandium was obtained. The solvent was allowed to evaporate, and the strip placed for about 10 minutes in an atmosphere of ammonia. The strip was sprayed with an alcoholic solution of alizarin and finally with N-acetic acid; thorium was then detected as a violet-blue band with a sharp front edge about 0·6 cm. behind the solvent front. Scandium formed a more diffuse band about 2·5 cm. in front of the rare earths which moved only slightly from the original position of the test spot. With alizarin the rare earths gave a similar colour to thorium but a redder tint was obtained with scandium. By this method 1 μg. of scandium was detected in 1000 μg. of the rare earths.

Scandium was also separated from the rare earths by using methyl acetate containing 10% (v/v) of water and 5% (v/v) of nitric acid (*d* 1·42) as solvent. The strip was allowed a solvent run of 25 cm.; scandium was then found in a similar position to that obtained with tetrahydrosylvan but in a narrower

band. Thorium, however, was detected as a more diffuse band between scandium and the solvent front.

(l) *Separation of* F, Cl, Br, *and* I. (With D. B. Rees Evans.)—*Recommended method.* The acid radicals are present as their sodium salts and the solvent used is pyridine containing 10% (v/v) of water.

The anions, fluoride, chloride, bromide, and iodide, have been separated as their sodium salts by using pyridine or acetone as solvent. The acetone used contained 20% (v/v) of water, and the pyridine was AnalaR pyridine, with 10% (v/v) of added water. Separations were not affected by a variation of ±2·5% in the water concentration of the solvents. The test solution, consisting of a neutral aqueous solution of sodium chloride, bromide, and iodide (the sodium salts were found preferable to the potassium salts), was spotted on a paper strip and allowed to dry in air. The strip was run in an atmosphere saturated with solvent vapour for 1½—2 hours. The solvent was allowed to evaporate from the strip which was then sprayed with a mixture of silver nitrate and fluorescein solutions. On drying, the halides appeared as three characteristic dark bands, which when viewed under ultra-violet light appeared as dark areas on a fluorescent background (Fig. 6; Strip IV). Strips one inch wide being used, it was possible to detect 1 μg. of bromide and 4 μg. of chloride or iodide in 0·05 ml. of original solution by this method. With a triangular strip, 1 μg. of chloride or iodide per 0·05 ml. of test solution was detected. Separations were carried out in which 1—10 μg. of one or two of the halides have been detected in the presence of 10 times the quantity of either one or both of the others. No difficulty has been experienced in dealing with concentrations up to 200 μg./0·05 ml. of each of the halides.

A more limited study has been made of the behaviour of fluoride. Sodium fluoride was added to the original solution of sodium chloride, bromide, and iodide. Strips were run with both the acetone and the pyridine solvent. The position of the fluoride band was detected by spraying with zirconium–alizarin reagent. For this purpose each strip was cut in two longitudinally; one part was then sprayed with silver nitrate–fluorescein reagent and the other with zirconium–alizarin solution. When pyridine was used as solvent the fluoride remained in the original spot. With the acetone solvent the fluoride moved but still remained separated from the chloride band. With this solvent a trace of fluoride was left in the original spot. Use of a wet spot overcame this disadvantage but R_F values were not then repeatable. R_F Values obtained by using a dry spot were fairly constant with both solvents as indicated below:

R_F *Values for halides.*

Radical.	Acetone + 20% (v/v) H_2O.				Pyridine + 10% (v/v) H_2O.			
Fluoride	—	—	0·26	0·24	—	—	0·00	0·00
Chloride	0·50	0·53	0·51	0·49	0·25	0·22	0·23	0·24
Bromide	0·62	0·62	0·62	0·60	0·47	0·47	0·47	0·47
Iodide	0·77	0·77	0·77	0·76	0·72	0·70	0·72	0·71

(m) *Miscellaneous Separations.* (With N. F. Kember.)—In addition to readily recognised groups of metals the separation of a number of special mixtures of metals has been examined, as follows: (1) The separation of nickel, manganese, cobalt, copper, and iron (of interest in analysis of steel) has been studied, the solvent being either acetone or methyl ethyl ketone mixtures with hydrochloric acid. (2) In parallel experiments, using the same solvents, the separation of uranium, vanadium, and titanium has been explored.

For this purpose two solutions were prepared, one containing nickel, manganese, cobalt, copper, and iron in dilute hydrochloric acid, and another containing uranium, vanadium, and titanium, also in dilute hydrochloric acid. A portion of each solution was placed upon a separate paper strip and allowed to dry in air; the solvent was then allowed to run down both strips for a distance of 15 cm. A series of approximate R_F values obtained with different solvents are shown in Table VI. It can be seen that nickel, manganese, cobalt, copper, and iron have been separated with methyl ethyl ketone + 8% (v/v) of hydrochloric acid (d 1·18), and uranium has been extracted from vanadium and titanium with a variety of solvents.

Two lines drawn between a pair of R_F values in the table indicate that the two metals concerned are in bands which overlap. One line indicates that the bands just touch. The abbreviations D or VD written after an R_F value indicate that the band is diffuse or very diffuse. Where two R_F values are given for the same metal then the metal is in a double band.

With methyl ethyl ketone as solvent two phases were obtained on the paper strip; acetone, although miscible with water, also gave two phases. With both solvents the phases consisted of a lower dry solvent phase, in which the acid concentration was low, and an upper phase of aqueous solvent in which there appeared to be an acidity gradient, the strip being most acid at the top and becoming progressively less acid nearer the solvent front. The approximate position of the interphase boundary was measured and the R_F value is recorded with those of the metals in Table VI. It appears to be directly related to the proportion of acid and water in the solvent, the ratio of the wet to dry solvent phase increasing as the concentration of acid is increased and falling off as the water content is increased. The position of the interphase boundary is important in that copper tends to split into two bands, a main band in the wet solvent phase and a weaker band in the dry solvent phase. If, however, the R_F value of the interphase boundary is sufficiently high, copper is found only in the wet solvent phase. The behaviour of uranium is also unusual in that it is sometimes found in the wet solvent phase and at others in the dry solvent phase.

During a study of the double band formation of copper it was noticed that the acid ketonic solvents used extracted a certain amount of copper and iron from the filter-paper. After runs on blank sheets and strips of paper, a band of iron was detected in the solvent front and some way behind a band of copper was obtained. Further investigations are being made to extract this soluble inorganic material without interfering with subsequent chromatographic separations.

TABLE VI.

R_F values with different solvents.

Solvent. / Metal.	$COMe_2$ + 5% (v/v) H_2O + 5% (v/v) HCl.	$COMe_2$ + 10% (v/v) H_2O + 5% (v/v) HCl.	COMeEt + 6% (v/v) HCl.	COMeEt + 8% (v/v) HCl.	COMeEt + 5% (v/v) H_2O + 8% (v/v) HCl.	COMeEt + 10% (v/v) H_2O + 10% (v/v) HCl.	COMeEt + 10% (v/v) H_2O + 5% (v/v) HCl.
Strip 1.							
Ni	0·09	0·12	0·01	0·01	0·01	0·10	0·005
Mn	0·21	0·29	0·13	0·18	0·13	0·13	0·01
Co	0·43	0·27	0·42D	0·54	0·30	0·21	0·04
Cu	0·61, 0·80	0·63, 0·92	0·65VD	0·71	0·72VD	0·63, 0·70D	0·26, 0·39
Fe	0·97	0·97	0·90	0·93	0·91	0·90	0·70VD
Strip 2.							
Ti	—	0·17	—	—	—	0·10	0·02
V	0·15	0·17	0·07	0·14	0·09	0·12	0·03
U	0·65	0·81	0·76	0·87	0·73	0·62	0·30
R_F value of interface...	0·64	0·64	0·50	0·82	0·72	0·64	0·37

(3) *Separations with Butyl Alcohol.*—The solvent butyl alcohol saturated with 3N-hydrochloric acid, used for the separation of the metals of the analytical group IIa, has been employed in a number of other separations. The members of the following pairs of metals are mutually interfering, when undergoing estimation on the polarograph : copper and bismuth, vanadium and iron, uranium and molybdenum, and lead and antimony; but, as may be deduced from the R_F values in the table below, separation is possible by using butyl alcohol saturated with 3N-hydrochloric acid. A chloride solution of the metals is treated as described in Section (a) (p. 518). After suitable development, copper, vanadium, uranium, and lead are found on the top portion of the strip, above the iron band below which the bismuth, molybdenum, and antimony bands are located. The individual members of each of these groups of four metals may then be estimated by the polarograph since the other three metals present will not interfere.

R_F Values with butyl alcohol + 3N-hydrochloric acid.

Metal	V	Cu	Pb	U	Fe	Mo	Bi	Sb
R_F value	0·18	0·19	0·23	0·26	0·42	0·53	0·57	0·78

Enhanced Colours.—It has been noticed that when a strip is sprayed with developing reagent before all the solvent has evaporated, the colours obtained are often very much more intense, than those obtained normally with the reagent and the radical after solvent has been removed, *e.g.*, arsenic, antimony, and tin with dithizone in chloroform in the presence of ethyl acetoacetate, scandium and the rare earths with alizarin in the presence of methyl acetate, gold and the platinum metals with stannous chloride in the presence of various " Carbitol " derivatives, the halides with silver nitrate and fluorescein in the presence of pyridine.

It is thought that this effect may have application in increasing the sensitivity of " spot " tests. The opposite effect has also been noticed. It is then often necessary to warm the strip for some time after developing it to allow the colour reaction to proceed.

Preparation of Solvents.—Acetone. Refluxed with solid potassium hydroxide and permanganate for 1 hour; the fraction, b. p. 56° ± 0·5°, was used.

Methyl ethyl ketone. As acetone. The fraction, b. p. 79·5—79·7°, was used.

Methyl n-propyl ketone. As acetone. The fraction, b. p. 99—102°, was used.

Methyl alcohol. Redistilled, b. p. 63°.

n-Butyl alcohol. Dried over calcium; b. p. 116·5—117·5°.

Amyl alcohol and pyridine. Both of AnalaR brand.

Ethyl acetate. Shaken with saturated calcium chloride solution, dried ($CaCl_2$), and distilled; b. p. 76·5—77·5°.

Methyl acetate. Either the constant-boiling mixture with methyl alcohol, b. p. 54°, was used, or the ester was dried ($CaCl_2$) and distilled, the fraction of b. p. 56·5—58° being used.

Ethyl ether. Refluxed with alkaline permanganate, distilled, dried ($CaCl_2$), and fractionated. The solvent used was free from peroxide and had a water content of less than 1%.

Tetrahydrofurfuran. As ethyl ether; the fraction of b. p. 79—80° was used.

DISCUSSION.

Measurement of R_F Values.—The method used for measuring R_F values requires explanation. The original solution was placed along a pencilled line ruled across the paper strip. The

distance moved by an element was considered to be the distance between this line and the "centre of gravity" of the band formed by the element; this was compared with the movement of the solvent measured from the same line. This method of measurement was simple but suffered from several disadvantages; no indication was given of the width of a band, without which an R_F value can be misleading, *e.g.*, using amyl alcohol as solvent the R_F values for cadmium and mercury were very close but the bands were so narrow that separation occurred, whereas with the same amounts of lead and copper and the same solvent, a difference in R_F values was obtained, but without separation, the lead forming a narrow band in the forward area of a wide copper band. An alternative method of measurement would be to give the R_F values for the front and the rear boundary of each band; this, however, would be difficult for those bands with diffuse boundaries. When two liquid phases are obtained on a paper strip there is some advantage to be gained from using the aqueous phase front (Lederer, *Nature*, 1948, **162**, 776) as a reference point for the calculation of R_F values, but in many cases the position of the phase front has been very indeterminate and in others only one phase appeared to exist.

Constancy of R_F *Values.*—Providing close control of all the variables is maintained, constant R_F values are obtained. The necessity for such close control would be a disadvantage in routine applications but, as found with amino-acids (Consden *et al.*, *loc. cit.*), relative rates of movement are constant with less control. Thus, one band on a strip can usually be identified by its position relative to known bands. Again, the large number of characteristic "spot" tests available for the detection of inorganic radicals diminishes the necessity for accurate measurement of R_F values. Constancy of solvents, temperature, and saturation of the atmosphere being assumed, a number of factors were found to affect R_F values, *viz.*:

(*a*) The presence of other anions. This is very common. A good example is the presence of chloride in separations carried out with nitrate solutions.

(*b*) The acidity of the original solution. This effect has been reported by Lacourt *et al.* (*loc. cit.*), and variations have been found although the original solution was first allowed to evaporate. The cause may be due to the need for acid in the formation of a complex soluble in the organic solvent complex, *e.g.*, gold chloride. On the other hand, the presence of acid may tend to prevent complex formation, *e.g.*, the extraction of mercury with methyl acetate from a strongly acid solution.

(*c*) The time of running of a strip. This factor is not important in all cases but is important in certain separations. In the separation of copper, lead, bismuth, cadmium, and mercury with butyl alcohol saturated with 3*N*-hydrochloric acid, R_F values increase with the time of running and this coincides with a decrease in the rate of movement of the solvent front. The reason for these changes is not known with certainty but several points may be relevant. At the beginning of a run, the paper is in equilibrium with the prevailing laboratory atmospheric conditions but after some twelve or more hours in an atmosphere saturated with respect to butyl alcohol and dilute hydrochloric acid the strip has absorbed so much water vapour that difficulty is often found in detecting the exact position of the solvent front. It is this increase in water content of the cellulose which undoubtedly accounts for the decrease in the rate of movement of the solvent front. A further variable which has not, so far, been investigated is the esterification of the butyl alcohol.

(*d*) The presence and concentration of other cations. A few cases of interference by one metal on the extraction of another have been observed. This appears to be due to complex-cation formation or to the amphoteric properties of one of the metals.

The Formation of Two Phases.—The following explanation is put forward to correlate all the facts observed. Consider a solvent containing water passing down a strip of paper. The cellulose will absorb water from the solvent until an equilibrium is set up. Since the affinity of cellulose for water is much higher than that of most organic solvents, equilibrium is reached when the solvent is almost dry and the cellulose almost saturated with water. This will result in a clearly defined wet area of strip, and further down the strip there is an area of dry solvent. If now the percentage of water in the solvent is progressively increased, the ratio of area of wet phase to area of dry phase increases. This type of behaviour was observed on adding increasing quantities of water to the constant-boiling mixture of methyl acetate and methyl alcohol used for the extraction of mercury.

A solvent containing hydrochloric acid as well as water may next be considered. In some cases the presence of hydrochloric acid in the solvent increases its affinity for water. At the same time there is partition of hydrochloric acid between the water in the cellulose and the solvent. The net result is that the solvent competes more effectively with the cellulose for the

water and travels further down the strip before losing all its water. This results in (1) a hydrochloric acid gradient in the wet part of the strip and a very low concentration of hydrochloric acid in the dry phase (both these effects can be noted in separations with acetone, hydrochloric acid, water mixtures); (2) a lower concentration of water in the wet phase area of the strip than that obtained when using an organic solvent containing water only; (3) a larger ratio of wet to dry phase on the strip. The last two points are supported by the behaviour of a number of solvents, *e.g.*, butyl alcohol, amyl alcohol, or methyl propyl ketone, with increasing hydrochloric acid content. The concentration of water in the paper underlying the wet phase decreases with increase of hydrochloric acid concentration until it is very difficult to detect the exact position of the interphase boundary. This change is accompanied by an increase in wet/dry phase ratio which continues until only one phase is obtained. These observations are illustrated by the behaviour of platinum on extraction with methyl propyl ketone containing hydrochloric acid.

Band Width.—Those salts which have a high solubility in organic solvents tend to be extracted in the solvent front. When this occurs, *e.g.*, mercuric chloride with methyl acetate, gold chloride with a mixture of ethyl ether and hydrochloric acid, and ferric chloride with acetone–hydrochloric acid mixtures, the width of the band in the solvent front is usually very much less than the width of the original spot. When two phases exist on a paper strip, a similar decrease in band width is sometimes noticed if a metal tends to travel just above the inter-phase boundary, *e.g.*, arsenious chloride with ethyl acetate–water mixtures. A somewhat different case arises when cadmium and mercury chlorides are extracted with butyl alcohol saturated with 3N-hydrochloric acid. Both form bands narrower than the original spot and neither is in the solvent front, although the cadmium is probably just above the interphase boundary. The second case is explicable if a soluble metallo-complex is formed only in the presence of a definite excess of water or acid concentration.

Further work is necessary to explain the other two cases.

It is hoped to devise more general separations when further basic knowledge of the behaviour of different salts with various solvents has been obtained.

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CHEMICAL RESEARCH LABORATORY,
TEDDINGTON, MIDDLESEX.

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101. *Studies of Seed Mucilages. Part V. Examination of a Polysaccharide extracted from the Seeds of* Plantago ovata *Forsk by Hot Water.*

By R. A. LAIDLAW and E. G. V. PERCIVAL.

Extraction of these seeds with hot water, after exhaustive extraction with cold water, yielded a polysaccharide fraction (PII, equiv., *ca.* 4000; uronic anhydride, *ca.* 3%; pentosan, *ca.* 90%; methylpentosan, nil). Hydrolysis of PII gave D-xylose (80%), L-arabinose (14%), D-galactose (a trace), an aldobiuronic acid (*ca.* 0·3%), and an insoluble residue (*ca.* 3%). Acetylation, deacetylation and methylation, and fractional precipitation gave products *A* (63%), *B* (32%), and C (5%). Methanolysis and hydrolysis of *A* gave trimethyl D-xylopyranose (8 parts), trimethyl L-arabofuranose (3 parts), tetramethyl D-galactopyranose (*ca.* 0·3%), a 2 : 6-dimethyl hexose (1 part), 2 : 4-dimethyl D-xylopyranose (4 parts), 3-methyl D-xylopyranose (8 parts), and D-xylopyranose (1 part).

IN Part III (Laidlaw and Percival, *J.*, 1949, 1600) the polysaccharide obtained from *Plantago ovata* Forsk seeds by extraction with cold water (PI) was shown to be highly complex. The main constituents liberated on hydrolysis were D-xylose (46%), L-arabinose (7%), and 2-D-galacturonosido-L-rhamnose (40%), but after acetylation and methylation no uronic acid residues remained. Although it was possible to indicate the mode of linkage of the xylose and arabinose residues in the methylated polysaccharide, it was thought that at least two associated polysaccharides were present in the mucilage, a polyuronide and a neutral fraction. This indeed agreed with Anderson and Fireman's observation (*J. Biol. Chem.*, 1935, **109**, 437) that products containing variable quantities of uronic acid residues could be isolated depending on purely mechanical differences in the mode of extraction. To throw further light on the matter, we

have studied the properties of the polysaccharide (PII) obtained by extraction of the seeds with hot water after exhaustive extraction with cold water. The proportion of uronic acid residues in PII is much less than in PI, the equivalent by titration being *ca.* 4000 (cf. 700 for PI), and PII contains only 3% of uronic anhydride; the pentosan content is correspondingly higher (90%) and L-rhamnose is absent. The uronic anhydride is considered to arise from an associated polyuronide. Hydrolysis of PII gave D-xylose (80%), L-arabinose (14%), a trace of galactose, and a small amount (0·3%) of a substance which appeared to be the barium salt of an aldobiuronic acid with properties different from that isolated from PI (*loc. cit.*).

Acetylation and methylation gave a methylated polysaccharide which was fractionated to give products *A*, *B*, and *C* (see table, p. 531). Products *A* and *B*, which together amounted to 95% of the methylated mucilage, appeared to be essentially similar, apart from the lower specific viscosity, and presumably, molecular weight of *B*.

Product *A*, on methanolysis afforded a mixture of methylated sugar glycosides which were separated by solvent extraction (Brown and Jones, *J.*, 1947, 1344) to give the four fractions discussed below, *viz.*, I (47·8%), II (15·7%), III (32·2%), and IV (4·4%). Fraction I was a mixture of trimethyl methyl-D-xylopyranosides and -L-arabofuranosides similar to that described previously (*loc. cit.*): crystalline trimethyl D-xylopyranose, its anilide, trimethyl D-xylopyranolactone, and 2 : 3 : 5-trimethyl L-arabonamide were isolated. From a consideration of the lactone equilibria it was estimated that trimethyl L-arabofuranose constituted about 14% of the products of hydrolysis of the methylated mucilage. Fraction II on hydrolysis and separation on a column of powdered cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) gave six fractions. Of these, fraction II(1) was identical with I; II(2) was tetramethyl D-galactopyranose; II(3) has not been identified although it appears to be a 2 : 6-dimethyl aldohexose; II(4) proved to be a mixture of 2 : 3-dimethyl and 2 : 4-dimethyl D-xylose. Complete methylation gave trimethyl D-xylopyranose as the sole product, and the mixed lactone obtained on oxidation, the equivalent weight of which by titration corresponded to a dimethyl pentonolactone, showed $[\alpha]_D^{17}$ $+30·8° \longrightarrow 45·2°$ (96 hours) corresponding to a mixture of 2 : 3-dimethyl D-xylofuranolactone (40%) and 2 : 4-dimethyl D-xylopyranolactone (60%). Oxidation of the mixed sodium salts with periodic acid (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1473) gave formaldehyde in amount corresponding to the presence of 38% of sodium 2 : 3-dimethyl xylonate, and the syrupy amide gave a negative Weerman test (*Rec. Trav. chim.*, 1917, **37**, 16). A crystalline anilide, m. p. 158°, obtained from fraction II(4) was identified as slightly impure 2 : 4-dimethyl D-xylose anilide.

Fraction II(5) crystallised completely to give 2 : 4-dimethyl β-D-xylose which was identified by the properties of its lactone, by the facts that the derived amide gave a negative Weerman test and yielded no formaldehyde on periodate oxidation, and by comparison with a standard on the paper chromatogram.

Fraction II(6) proved to be 3-methyl xylose.

Fraction II(3) has defied identification; a syrup having $[\alpha]_D -19°$, it was readily oxidised by sodium hypoiodite and was thus an aldose. Oxidation gave a furanolactone {$[\alpha]_D -50° \longrightarrow -33°$ (18 days)}, showing the hydroxyl group on $C_{(4)}$ to be free. The derived crystalline *amide*, which analysis showed to be a dimethylhexonamide, gave a negative Weerman test showing the presence of a methoxyl group on $C_{(2)}$. The R_6 value (Hirst and Jones, *J.*, 1949, 928) of fraction II(3), 0·80, is higher than that for any dimethyl hexose recorded so far, but the brown colour formed with aniline oxalate was easily distinguishable from the pink colour given by pentose derivatives. Oxidation with periodic acid (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456) gave no acetaldehyde which, since the hydroxyl on $C_{(4)}$ is free, excludes all (except 5-substituted) 6-deoxyhexoses, in any event an unlikely possibility. No formaldehyde was released on oxidation with periodate (Reeves, *loc. cit.*) and this, coupled with the knowledge that the hydroxyl group on $C_{(4)}$ is free, makes it probable that a methoxyl group resides on $C_{(6)}$. That fraction II(3) was an individual substance appeared likely from the definition of the spot on the paper chromatogram and the isolation of a crystalline amide; complete methylation and hydrolysis gave a syrup which again gave a single spot on the chromatogram, although this observation would not exclude the presence of a mixture of D- and L-forms. The R_6 value observed (0·96) for the last-mentioned product appears to exclude tetramethyl galactopyranose (R_6 0·88); this is confirmed by the failure to isolate a tetramethyl hexose anilide which also seems to remove the possibility of the parent sugar being mannose. The examination of the original hydrolysed PII on the paper chromatogram seems to exclude idose and talose as possibilities. Gulose on the other hand has the same R_6 value as arabinose and would, therefore, escape detection, but gulose has not, so far, been isolated from a natural product.

Fraction III on hydrolysis and fractionation on a cellulose column gave four fractions as follows: III(*a*) having R_6 0·7; III(*b*), III(*c*), and III(*d*), having R_6 0·39.

Fraction III(*a*) gave a syrupy lactone {$[\alpha]_D^{20}$ +12° ⟶ +27° (50 hours)}, and the derived amide gave a negative Weerman reaction and a 20% yield of formaldehyde on periodate oxidation. Examination on the paper chromatogram showed III(*a*) to contain a mixture of 2 : 3-dimethyl and 2 : 4-dimethyl xylose, and from the above evidence the relative proportions were taken as 1 : 4. Faint traces of II(3) and of a monomethyl xylose were also present. Fraction III(*b*) crystallised to give 3-methyl D-xylose (80%), together with a syrup which, on oxidation, gave crystalline 3-methyl D-xylofuranolactone as the only product. Fraction III(*d*) gave the same crystalline lactone on suitable treatment, and III(*c*) gave crystalline 3-methyl xylose anilide. No 2-methyl xylose derivatives were detected, although they occurred in the products of hydrolysis of methylated PI (Part III, *loc. cit.*).

Fraction IV consisted almost entirely of methyl D-xylosides, chromatographic analysis of the hydrolysed syrup giving one spot only, corresponding to xylose, and the identity of D-xylose was confirmed as the crystalline dibenzylidene dimethylacetal (Breddy and Jones, *J.*, 1945, 738).

On the methanolysis of product *B* and separation by solvent extraction, five fractions were obtained which on qualitative examination by paper chromatography appeared closely similar to the fractions obtained from *A*, and no other individual sugars were present.

Allowing for the demethylation known to occur during methanolysis (Part III, *loc. cit.*) it was calculated that product *A* on hydrolysis gave trimethyl D-xylopyranose (8 parts), trimethyl L-arabofuranose (3 parts), tetramethyl D-galactopyranose (*ca.* 0·3%), 2 : 6-dimethyl hexose (1 part), 2 : 3-dimethyl D-xylopyranose (1 part), 2 : 4-dimethyl D-xylose (4 parts), 3-methyl D-xylopyranose (8 parts), and D-xylopyranose (1 part). Thus, in the polysaccharide the following units must be present, linked as shown:

$$\begin{matrix} & & & & & & & & & 1 \\ \text{X1;} & \text{A1;} & \text{G1;} & \text{3H4 (or 3H5);} & & \text{X3;} & \text{X4;} & \text{4X2;} & & \text{4X2} \\ & & & & & & & & & \mathbf{3} \end{matrix}$$

{X = D-xylopyranose; G = D-galactopyranose;
A = L-arabofuranose; H = hexose.}

No information is available at present to show how these units are related in the mucilage molecule. Thus, no definite structural formula can be assigned to the PII repeating unit, but the formula indicated below, one of many possible variants, would explain the properties of the methylated polysaccharide.

$$\begin{matrix} & & \mathbf{X} & & & & & & & & & & & & \\ & & \mathbf{1} & & & & & & & & & & & & \\ & & \mathbf{2} & & & & & & & & & & & & \\ \text{X1} & & \mathbf{4X} & & \mathbf{X} & & \mathbf{X} & & \mathbf{X} & & \mathbf{A} & & \mathbf{A} & & \mathbf{A} & \mathbf{X} \\ & & \mathbf{1} & & \mathbf{1} & & \mathbf{1} & & \mathbf{1} & & \mathbf{1} & & \mathbf{1} & & \mathbf{1} & \mathbf{1} \\ & & \mathbf{3} & & \mathbf{4} & & \mathbf{4} & & \mathbf{4} & & \mathbf{4} & & \mathbf{4} & & \mathbf{4} & \mathbf{4} \\ \ldots & \text{1X2} & \text{1H3} & \text{1X3} & \text{1X2} & \text{1X3} & \text{1X2} & \text{1X4} & \text{1X2} & \text{1X3} & \text{1X2} & \text{1X3} & \text{1X2} & \text{1X2} & \ldots & \cdot \\ & & \mathbf{4} & & & & & & & & & & & & & \\ & & \mathbf{1} & & & & & & & & & & & & & \\ \text{X1} & & \mathbf{2X} & & & & & & & & & & & & & \\ & & \mathbf{4} & & & & & & & & & & & & & \\ & & \mathbf{1} & & & & & & & & & & & & & \\ & & \mathbf{X} & & & & & & & & & & & & & \end{matrix}$$

X = D-xylopyranose; A = L-arabofuranose.

The galactose end-groups have been neglected in this formula, but it may be that in the mucilage molecule we have 13—14 such repeating units linked together and terminated by a D-galactopyranose residue.

Such a repeating unit should yield on oxidation with potassium periodate (Halsall, Hirst, and Jones, *J.*, 1947, 1427) 8 moles of formic acid, from the xylopyranose end-groups, *i.e.*, 0·00225 mol./g. The value found in practice for PII was 0·00234 mol./g., in good agreement with the theoretical figure. Further, a molecule of this constitution would use 20 moles of periodate or 0·00563 mol./g. The experimental figure (0·00535 mol./g. after 15 minutes when the initial rapid uptake appears to be complete) is in reasonable agreement. The higher figure (0·00674 mol./g.) obtained after 3 days may possibly be due to over-oxidation.

We may now compare the results from PII with those from PI. Methylated PI on hydrolysis yielded 2 : 3 : 4-trimethyl D-xylose (6 parts), 2 : 3 : 5-trimethyl L-arabinose (1 part), 2 : 4-dimethyl D-xylose (1 part), 3-methyl D-xylopyranose (4 parts), 2-methyl D-xylopyranose (1 part), and D-xylopyranose (2 parts). Thus, though we have in each case the same type of highly-branched structure considerable differences in detail are evident. Approximately the same

proportion of end-groups is present in each case, but in PII the amount of arabinose derivatives is doubled at the expense of the xylose derivatives. Again, PII appears to contain a much higher proportion of doubly-linked xylose units; 1 : 4-linked D-xylose, present in PII, could not be identified in PI, though it was found in the mucilage from *P. lanceolata* (Percival and Willox, Part IV, *J.*, 1949, 1607). Further, neither 2-methyl xylose could be obtained from methylated PII, and the proportion of D-xylose units linked through four positions was much less than in PI. Finally, no methylated derivatives of D-galactose, nor the unknown hexose, obtained from PII, were isolated from PI. Thus, PI and PII are to be regarded as distinct polysaccharides; it may well be that each of these is in itself a mixture of closely-related polysaccharides, but there is no evidence that they could be mixtures of relatively simple xylans and arabans constituted from single sugar units. The relatively high yield of L-arabinose obtained on the hydrolysis of PII, its correspondence with the yield of trimethyl methylarabofuranosides obtained on methanolysis of the methylated polysaccharide, and the failure to detect any partly methylated L-arabinose derivatives in the hydrolysis of either methylated PI or methylated PII prove that the arabinose units occur as end groups as, for example, in gum arabic (Smith, *J.*, 1940, 1035) and are not derived from an associated araban.

Experimental.

Evaporations were conducted under diminished pressure unless otherwise stated. Temperatures are bath-temperatures. Fractions from the cellulose column were evaporated to dryness, dissolved in water, digested with charcoal, and filtered hot; the aqueous solution was then evaporated to dryness and exhaustively extracted with boiling acetone, and the extracts were evaporated to dryness.

Preparation of PII.—Product PI was removed from the seeds by extraction (Part III, *loc. cit.*), and the seeds were washed continuously with cold water until no more mucilage was removed. The residue was then extracted with hot water (90—95°), and the highly viscous solution separated by filtration through muslin. The filtrate, on cooling, set to a gel from which the mucilage was precipitated by the addition of acidified ethanol (4 volumes; 20 c.c. of concentrated hydrochloric acid per l.). The fibrous product was dried with ethanol and ether and in a vacuum over phosphoric oxide (Found: equiv., by titration, *ca.* 4000; uronic acid, *ca.* 3%; pentosan, 90%; methylpentosan, nil; ash, 1·41%, unchanged on treatment with sulphuric acid). Precipitation with ethanol alone yielded a product with 1·46% of ash (as sulphate, 1·83%).

Hydrolysis of PII with Oxalic Acid.—The dry mucilage (1·502 g.) was hydrolysed with oxalic acid (3%; 75 c.c.) at 100°. $[\alpha]_D^{17}$ was −11° (1 hour); +12·5° (2 hours); +25° (3 hours); +38° (6 hours); +40° (52 hours, constant). A larger quantity (46·92 g.) was hydrolysed as above for 6 hours. The insoluble residue (1·43 g.) was removed and the filtrate neutralised with barium carbonate, filtered, and evaporated to 200 c.c. This solution was filtered into ethanol (2 l.) to give a white barium salt (X) (0·19 g.). Evaporation of the alcoholic solution yielded a reducing syrup (S) (43·5 g.). The salt X showed Ba, 15·4% and $[\alpha]_D^{17}$ +39° in water (*c*, 1·0). Syrup S partly crystallised. Trituration of the mixture (22·47 g.) with glacial acetic acid gave D-xylose (7·02 g.) which, on recrystallisation from ethanol showed m. p. and mixed m. p. 140° and $[\alpha]_D^{17}$ +80° falling to +20° after 4 hours in water and yielded xylosazone, m. p. and mixed m. p. 157°. Evaporation of the acetic acid washings gave a syrup (S′) (15·46 g.), a portion of which was treated with phenylmethylhydrazine. No precipitate of galactose phenylmethylhydrazone was obtained.

Syrup S′, on treatment with diphenylhydrazine, yielded L-arabinose diphenylhydrazone, m. p. 194° not depressed on admixture with an authentic specimen, in an amount corresponding to the presence of 14·2% of anhydroarabinose in the mucilage.

Paper chromatographic investigations of S′ indicated the presence of xylose and arabinose along with a trace of galactose.

Acetylation.—The product PII (45 g.) was moistened with ethanol and dispersed with shaking in pyridine (750 c.c.), and acetic anhydride (500 c.c.) was added slowly with continuous stirring. The mixture was then heated at 100° for 3 hours and left at room temperature for a further 48 hours, whereafter the acetate was precipitated by pouring the mixture into water (10 l.) and washed thoroughly in running water till free from pyridine. Yield, 60 g. (Found: $CH_3{\cdot}CO$, 30·9%). The properties of this material were unchanged on reacetylation.

Methylation.—The acetate was methylated directly in three 20-g. portions with methyl sulphate and sodium hydroxide as described in Part III (*loc. cit.*), each portion receiving four methylations. The products were combined and dissolved in chloroform, the solution was dried (Na_2SO_4), and the methylated polysaccharide fractionally precipitated by the addition of light petroleum (b. p. 40—60°), to give the fractions listed in the table.

Fraction.	Yield, g.	OMe, %.	$[\alpha]_D^{20}$ ($CHCl_3$).	η_{sp}^{20}/c'.*
A	20·0	35·8	−121°	55·5
B	10·0	35·8	−120	19·3
C	1·6	27·1	−112	very low

* *c′* is the concentration in g.-mols. of methylated anhydroxylose residues per l.

Fraction *C* was obtained by evaporation of the residual solution almost to dryness and subsequent trituration with light petroleum. The properties of *A* and *B* were unchanged on further methylation. Neither *A* nor *B*, nor *C* contained any appreciable amount of uronic acid.

Hydrolysis of the Methylated Polysaccharide.—Fraction *A* (18·7 g.) was hydrolysed with methanolic hydrogen chloride (3%; 350 c.c.) for 21 hours at 80°. After neutralisation with silver carbonate, filtration, and evaporation, a non-reducing syrup (21·1 g.) was obtained.

Fractionation by Solvent Extraction.—The above syrup (20·4 g.) was dissolved in water (50 c.c.) and extracted with light petroleum (b. p. 38—40°) for 16 hours to give fraction I (9·725 g.), η_D^{17} 1·4423. Extraction with the same solvent for a further 210 hours gave fraction II (3·207 g.), η_D^{17} 1·4577. The residual aqueous solution was then extracted with chloroform for 20 hours to yield fraction III (6·571 g.), η_D^{16} 1·4722. Evaporation of the residue gave fraction IV (0·888 g.), η_D^{17} 1·4840. Recovery was 100%.

Hydrolysis and Fractionation of Fraction B.—Fraction B (9·1 g.) on methanolysis as above yielded a syrup (10·1 g.). Separation of the glycosides was again effected by solvent extraction. Thus, the syrup (8·95 g.) yielded, with light petroleum, fractions V (14 hours) (3·944 g.), η_D^{16} 1·4413, VI (+ 7 hours) (0·201 g.), η_D^{16} 1·4545, and VII (+ 90 hours) (0·745 g.), η_D^{16} 1·4580. Chloroform gave fraction VIII (17 hours) (2·655 g.), η_D^{16} 1·4675, and evaporation of the aqueous residue furnished fraction IX (1·375 g.), η_D^{16} 1·4683. Recovery was 8·920 g. (99·7%).

Examination of Fraction I.—Fraction I (9·04 g.) was hydrolysed with nitric acid (2%; 150 c.c.) at 100°. $[\alpha]_D^{17}$ were +19° (1 hour); +7° (3 hours); +4° (6 hours, constant). Neutralisation with barium carbonate, filtration, and evaporation of the filtrate left a residue which was exhaustively extracted with boiling acetone. The acetone extracts were combined and evaporated to yield a reducing syrup (6·97 g.). Several crops (total, 2·63 g.) of crystalline material were removed during a prolonged period, which on recrystallisation from ether gave trimethyl α-D-xylopyranose, m. p. and mixed m. p. 92°, $[\alpha]_D^{17}$ +63° (2 minutes), +33° (30 minutes), +19° (2 hours, constant) (*c*, 1·43 in water) (Found: C, 50·2; H, 8·1; OMe, 47·9. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·4; OMe, 48·4%). With alcoholic aniline the characteristic trimethyl D-xylose anilide was obtained (Part III, *loc. cit.*), m. p. and mixed m. p. 98° and $[\alpha]_D^{17}$ −84° (4 minutes), −70° (45 minutes), −44° (90 minutes), +34° (345 minutes), +47° (24 hours, constant) (*c*, 0·32 in ethanol). The residual syrup (3·48 g.) was examined on the paper chromatogram which indicated the presence of trimethyl xylose and/or trimethyl arabinose, along with traces of other components.

Attempted Separation on a Column of Cellulose.—The residual syrup (cf. preceding paragraph) (3·40 g.) was fractionated on a column of cellulose (15″ × 1·2″) (Hough, Jones, and Wadman, *loc. cit.*), the eluent being light petroleum (b. p. 100—120°)-butanol (7 : 3) saturated with water. Four main fractions were collected: (i) 1·00 g., $[\alpha]_D^{17}$ −10° (*c* 2·67 in water); (ii) 1·13 g., $[\alpha]_D^{17}$ −11° (*c*, 3·25 in water); (iii) 0·55 g., $[\alpha]_D^{17}$ −5° (*c*, 1·57 in water) (these three gave spots on the paper chromatogram corresponding to trimethyl xylose and/or trimethyl arabinose); (iv) 0·27 g., obviously composed of less fully methylated materials. Recovery was 2·95 g. (87%). Syrups (i), (ii), and (iii) were recombined (2·30 g.), dissolved in water, and oxidised at room temperature with bromine till non-reducing (4 days). After treatment with silver carbonate and hydrogen sulphide, evaporation gave a syrupy product which was fractionally distilled to give (*a*) 1·06 g., b. p. 95—105°/0·01 mm., η_D^{16} 1·4496 (Found: OMe, 48·4. Calc. for $C_8H_{14}O_5$: OMe, 48·9%), and (*b*) 0·82 g., b. p. 105—125°, η_D^{16} 1·4551 (Found: OMe, 47·6%). Portion (*a*) showed $[\alpha]_D^{17}$ −25° (5 minutes), −24° (1 hour), −21° (31 hours), −14° (100 hours), −11° (200 hours), −10° (314 hours, constant) (*c*, 3·14 in water). Portion (*a*) (62·6 mg.) required 5·50 c.c. of 0·0565N-sodium hydroxide for neutralisation to phenolphthalein (Calc. for $C_8H_{14}O_5$: 5·84 c.c.) and on treatment with methanolic ammonia yielded crystalline 2 : 3 : 5-trimethyl L-arabonamide. On recrystallisation (ethyl acetate) this showed m. p. and mixed m. p. 136° and $[\alpha]_D^{17}$ +21° (*c*, 1·41 in water) (Found: C, 46·0; H, 8·05; N, 6·95; OMe, 43·7. Calc. for $C_8H_{17}O_5N$: C, 46·3; H, 8·3; N, 6·8; OMe, 44·9%). Portion (*b*) showed $[\alpha]_D^{17}$ −9° (5 minutes), −8° (4 hours), −4° (29 hours), +3° (100 hours), +6° (200 hours, constant) (*c*, 3·451 in water); 34·5 mg. required 2·95 c.c. of 0·0565N-sodium hydroxide for neutralisation (Calc. for $C_8H_{14}O_5$: 3·21 c.c.). It gave a syrupy amide, $[\alpha]_D^{16}$ +35° (*c*, 2·94 in water). Portion (*b*) partly crystallised when kept, to yield 2 : 3 : 4-trimethyl xylopyranolactone, m. p. and mixed m. p. 50° (Found: C, 50·6; H, 7·5; OMe, 48·1. Calc. for $C_8H_{14}O_5$: C, 50·6; H, 7·4; OMe, 48·9%).

Examination of Fraction II.—Fraction II (3·20 g.) was hydrolysed with nitric acid (2%; 100 c.c.) at 100°: $[\alpha]_D^{17}$ +28° (1 hour); +22° (2 hours); +16° (4 hours); +14° (6 hours, constant). Appropriate treatment gave a reducing syrup (2·65 g.). This syrup (2·5 g.) was combined with column-fraction (iv) from fraction I above, and fractionation effected on a column of cellulose (27″ × 1·2″) as before. This gave: (1) 0·11 g., R_{Me} 0·94, (2) 0·065 g. (0·88), (3) 0·56 g. (0·80), (4) 0·69 g. (0·74), and (5) 0·59 g. (0·66); a further fraction, (6) 0·14 g. (0·39), was obtained by washing the column with water. Recovery was 2·16 g. (76·4%).

Fraction (1). This corresponded to fraction I.

Fraction (2). On treatment with alcoholic aniline this yielded 2″ 3 : 4 : 6-tetramethyl D-galactose anilide, m. p. 189°, not depressed on admixture with an authentic specimen (Found: OMe, 39·1. Calc. for $C_{14}H_{22}O_5N$: OMe, 39·9%).

Fraction (3). The syrup showed OMe, 33·6% and $[\alpha]_D^{17}$ −19° (*c* 1·35 in water). On the paper chromatogram it gave a brown spot when sprayed with aqueous aniline oxalate and heated. Oxidation was easily effected with alkaline hypoiodite under standard conditions (Found: *M*, 180. Calc. for $C_8H_{14}O_6$: *M*, 208). A test oxidation on D-glucose gave *M*, 180 (Calc. for $C_6H_{12}O_6$: *M*, 180). Fraction (3) failed to form a crystalline anilide.

The syrup (3) (0·118) was kept at 80° with 1% methanolic hydrogen chloride. $[\alpha]_D^{17}$ was −75° (40 minutes) and −82° (230 minutes, constant).

Methylation.—Neutralisation with silver carbonate, filtration, and evaporation yielded a non-reducing syrup which was methylated 3 times with the Purdie reagents, and the highly mobile syrupy product distilled at 80°/0·01 mm. The distillate (43 mg.; OMe, 58·1%) was hydrolysed with nitric acid (2%; 10 c.c.) at 100°. $[\alpha]_D^{17}$ was −64° (zero time), −41° (50 minutes), −34° (2 hours, constant) (Calc. as methyliglycosides). Appropriate treatment gave the free sugar as a syrup (20 mg.) which failed to crystallise. On investigation by means of the paper chromatogram this showed one spot only at R_{Me} 0·96. No crystalline anilide could be obtained.

Lactone Formation.—Fraction (3) (0·11 g.) was converted into the lactone. The product (70 mg.)

did not crystallise (Found: OMe, 22·6%). $[\alpha]_D^{19}$ was −50° (10 minutes), −46° (95 hours), −36° (263 hours), −33° (432 hours, constant) (*c*, 0·606 in water). The lactone (9·1 mg.) required 2·08 c.c. of 0·0249N-sodium hydroxide for neutralisation (Calc. for $C_6H_{14}O_5$: 1·80 c.c.).

Amide Formation.—The above lactone was reclaimed from polarimetric solution by evaporation and redistillation. A portion of this material (50 mg.) was converted into the amide. A white crystalline solid was obtained, which on recrystallisation (ethyl acetate) had m. p. 131—132° and gave a negative Weerman test (Found: C, 42·9; H, 7·7; N, 6·8; OMe, 30·0. Calc. for $C_9H_{19}O_5N$: C, 43·0; H, 7·7; N, 6·3; OMe, 27·8%).

Periodate Oxidations.—The free sugar (15·2 mg.) was oxidised according to the method of Nicolet and Shinn (*loc. cit.*). No acetaldehyde was detected, whereas L-rhamnose (16·0 mg.) gave acetaldehyde in 90% yield.

Fraction (3) (19·0 mg.) was oxidised according to the method of Reeves (*loc. cit.*), but no formaldehyde was produced. A sample of D-xylose (17·0 mg.) under the same conditions yielded the formaldehyde–dimedon compound (12·5 mg.), m. p. and mixed m. p. 187°.

Fraction (4).—This was a syrup which showed $[\alpha]_D^{19}$ +16° (*c*, 3·85 in water) and OMe, 33·7%. On the paper chromatogram a pink colour was obtained on spraying of the spot with aniline oxalate and heating.

Anilide Formation.—Treatment of the syrupy fraction (4) (20 mg.) with alcoholic aniline gave a crystalline product, which, on recrystallisation (acetone–ether–light petroleum) had m. p. 158°, mixed m. p. with 2 : 3-dimethyl D-xylose anilide, 128° (Found: OMe, 28·0. Calc. for $C_{13}H_{19}O_4N$: OMe, 24·9%).

Lactone Formation.—Lactonisation of the syrup (0·3 g.) and distillation gave a syrupy product (0·21 g.) which showed $[\alpha]_D^{17}$ +30·8° (7 minutes); +38·4° (20 hours); +44·2° (48 hours); +45·2° (96 hours, constant) (*c*, 1·04 in water). A portion of the lactone was twice redistilled, but no significant difference in rotation figures was observed (Found: OMe, 33·6. Calc. for $C_7H_{12}O_5$: OMe, 35·3%). The lactone (20·8 mg.) required 4·80 c.c. of 0·0249N-sodium hydroxide for neutralisation (calc. for $C_7H_{12}O_5$: 4·75 c.c.). The lactone (41·0 mg.) was heated with sodium hydroxide (1N.; 0·5 c.c.) at 50° for 15 minutes. Water (1·5 c.c.) was added and the solution treated with periodic acid (Reeves, *loc. cit.*). This treatment gave the formaldehyde–dimedon compound (26·0 mg.), m. p. and mixed m. p. 188°. Treatment of the lactone with methanolic ammonia gave a syrupy amide, $[\alpha]_D^{17}$ +43° (*c*, 0·63 in water), which showed a negative Weerman test.

Methylation.—Fraction (4) (85 mg.) was treated with methanolic hydrogen chloride (3%; 20 c.c.) at 80° for 15 hours, to give a non-reducing syrup which was methylated 3 times with silver oxide and methyl iodide. The prodnct on distillation at 80—100°/0·01 mm. was a highly mobile syrup (29 mg.) (Found: OMe, 58·4%). Hydrolysis was effected with nitric acid (2%; 7 c.c.) at 100°. $[\alpha]_D^{19}$ was +41° (zero time); +31° (1 hour); +15° (3 hours, constant). Appropriate treatment gave a syrup (17 mg.) identified on the paper chromatogram as trimethyl xylopyranose.

Fraction (5).—This crystallised completely. Trituration with acetone–light petroleum (1 : 3) gave 2 : 4-dimethyl β-D-xylose, m. p. 111°, not depressed on admixture with an authentic specimen. $[\alpha]_D^{19}$ was −13° (7 minutes); −1·5° (17 minutes); +9° (31 minutes); +19° (64 minutes); +21·5° (3 hours); +23° (24 hours, constant) (*c*, 2·1 in water) (Found: C, 47·3; H, 7·75; OMe, 34·7. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9; OMe, 34·8%). Lactonisation of this material gave syrupy 2 : 4-dimethyl xylonolactone, $[\alpha]_D^{17}$ −12° (15 minutes); −9° (2½ hours); +15° (22 hours); +26° (46 hours); +27° (120 hours, constant) (*c*, 1·90 in water) (Barker, Hirst, and Jones, *loc. cit.*). Treatment with methanolic ammonia gave the syrupy amide, which showed a negative Weerman test, and on oxidation with periodic acid gave no formaldehyde.

Examination of Fraction (6).—Paper chromatography indicated the presence of 3-methyl xylose only, by direct comparison with a control. $[\alpha]_D^{19}$ +23° (*c*, 1·52 in water) was recorded.

Examination of Fraction III.—Fraction III (6·56 g.) was hydrolysed with nitric acid (2%; 150 c.c.) at 100°. $[\alpha]_D^{19}$ was +39° (1 hour); +24° (3 hours); +19° (6 hours, constant). This yielded a reducing syrup (4·92 g.) (Found: OMe, 18·2%). A fractionation was effected by means of a column of cellulose (27″ × 1·2″) with butanol (60%)–light petroleum (40%) saturated with water as eluent, to give four main fractions: (*a*) 0·95 g., (*b*) 2·26 g., (*c*) 0·44 g., and (*d*) 0·60 g. Recovery was 4·25 g. (92%).

Fraction (*a*), on examination by the paper chromatogram, was shown to consist mainly of 2 : 4-dimethyl xylose, with some 2 : 3-dimethyl xylose and a trace of the 2 : 6-dimethyl hexose component, while fractions (*b*), (*c*), and (*d*) showed the presence of monomethyl xyloses and/or arabinoses only.

Fraction (*a*) (0·80 g.) was oxidised, and distillation at 140—160°/0·05 mm. gave a syrupy lactone (0·53 g.) (Found: OMe, 33·4. Calc. for $C_7H_{12}O_5$: OMe, 34·8%). $[\alpha]_D^{19}$ +12° (5 minutes); +13·5° (1 hour); +15° (5 hours); +24° (24 hours); +27° (50 hours, constant) (*c*, 1·265 in water). The lactone (12·65 mg.) required 2·98 c.c. of 0·0249N-sodium hydroxide for neutralisation (Calc. for $C_7H_{12}O_5$: 2·89 c.c.). Treatment with methanolic ammonia yielded a syrupy amide which gave a negative Weerman test. Oxidation (of 41 mg.) with periodic acid gave formaldehyde as the dimedon compound (13 mg.), m. p. and mixed m. p. 187°.

Fraction (*b*) partly crystallised when kept. The crystalline material (1·50 g.) was separated by drainage on a tile and showed $[\alpha]_D^{17}$ +45° (5 minutes); +32° (17 minutes); +23° (50 minutes); +19° (19 minutes, constant) (*c*, 1·58 in water). Recrystallisation (absolute ethanol) gave 3-methyl D-xylopyranose as hygroscopic white needles, m. p. 95°, not depressed on admixture with an authentic specimen (Found: C, 42·7; H, 7·4; OMe, 21·0. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·4; OMe, 18·9%). Exhaustive extraction, with boiling acetone, of the tile used in separating the crystalline component gave a syrup (0·40 g.), $[\alpha]_D^{17}$ +25° (*c*, 4·0 in water), which was oxidised to the lactone. Distillation at 160—170°/0·025 mm. gave 3-methyl γ-D-xylonolactone (0·20 g.) as a syrup which rapidly crystallised. On recrystallisation (ethyl acetate–light petroleum), this had m. p. 90°, not depressed on admixture with an authentic specimen; $[\alpha]_D^{17}$ +72° (zero time); +45° (245 hours); +40° (600 hours, constant) (*c*, 0·88 in water) (Found: OMe, 18·0. Calc. for $C_6H_{12}O_5$: OMe, 19·1%).

Fraction (*c*) (0·22 g.), on treatment with alcoholic aniline, gave crystalline 3-methyl D-xylose anilide as the sole product, which on recrystallisation from ethyl acetate had m. p. and mixed m. p. 137° (Found:

C, 59·9; H, 7·1; N, 5·65; OMe, 12·5. Calc. for $C_{12}H_{17}O_8N$: C, 60·2; H, 7·2; N, 5·9; OMe, 12·9%).

Fraction (*d*) (0·40 g.) was oxidised to the lactone. The product was crystalline 3-methyl γ-D-xylonolactone, m. p. and mixed m. p. 94°, $[\alpha]_D^{20}$ +73° (5 minutes); +67° (6 hours); +63° (27 hours); +54° (120 hours); +48° (246 hours); +39° (510 hours, constant) (*c*, 0·685 in water). The lactone (8·22 mg.) required 2·20 c.c. of 0·0240N-sodium hydroxide for neutralisation (Calc. for $C_6H_{10}O_5$: 2·04 c.c.) (Found: C, 44·0; H, 6·47; OMe, 17·5. Calc. for $C_7H_{12}O_5$: C, 44·4; H, 6·2; OMe, 19·1%).

Examination of Fraction IV.—Fraction IV (0·88 g.) was hydrolysed with nitric acid (2%; 50 c.c.) at 100°. $[\alpha]_D^{20}$ was +41·5° (zero time); +32° (1 hour); +18° (3 hours); +15° (5 hours, constant). The solution was neutralised with barium carbonate, filtered, evaporated to dryness, and exhaustively extracted with boiling absolute methanol. The extracts were combined, evaporated to small volume, refiltered, and evaporated to dryness, to give a reducing syrup (0·70 g.) (Found: OMe, nil). Examination by means of the paper chromatogram gave xylose only, and the presence of D-xylose was confirmed by the isolation of the crystalline dimethyl acetal, m. p. and mixed m. p. 206°, of dibenzylidene D-xylose.

Examination of Fraction V.—Fraction V (3·93 g.) was hydrolysed with nitric acid as before. $[\alpha]_D^{17}$ was +18° (70 minutes); +7° (3 hours); +5° (6 hours, constant). This gave a reducing syrup (3·00 g.) which partly crystallised to give trimethyl α-D-xylopyranose (1·50 g.), m. p. and mixed m. p. 89°. The residual syrup (1·08 g.) on the paper chromatogram indicated trimethyl xylose and/or trimethyl arabinose along with small amounts of components of fraction VI.

Examination of Fraction VI.—Fraction VI (0·20 g.) was hydrolysed with nitric acid. $[\alpha]_D^{17}$ was +24° (1 hour); +18·5° (3 hours); +16° (5 hours, constant). This gave a reducing syrup (0·15 g.), which on the paper chromatogram indicated presence of trimethyl xylose and/or trimethyl arabinose (trace), tetramethyl galactose (trace), 2 : 6-dimethyl hexose, 2 : 3-dimethyl xylose, 2 : 4-dimethyl xylose, and 3-methyl xylose (trace).

Examination of Fraction VII.—Fraction VII (0·74 g.) was hydrolysed with nitric acid. $[\alpha]_D^{17}$ was +24° (1 hour); +17° (2 hours); +14° (4 hours); +13° (6 hours, constant). The syrup (0·54 g.) obtained, on investigation by means of the paper chromatogram, was found to contain the same components as fraction II.

Examination of Fractions VIII and IX.—These syrups were combined and the product (4·01 g.) hydrolysed with nitric acid. $[\alpha]_D^{18}$ was +34° (1 hour); +22° (3 hours); +18° (6 hours, constant). Appropriate treatment gave a syrup (3·00 g.) which, on investigation by the paper chromatogram, disclosed xylose, 3-methyl xylose, and smaller amounts of 2 : 4-dimethyl xylose, 2 : 3-dimethyl xylose, and 2 : 6-dimethyl hexose.

Formic Acid from PII.—The polysaccharide was oxidised with potassium periodate (Halsall, Hirst, and Jones, *J.*, 1947, 1427), and the formic acid liberated was determined by titration with 0·01N-sodium hydroxide with the following results, expressed in mols. of formic acid/g.: 0·00129 (1 day); 0·00182 (3 days); 0·00217 (6 days); 0·00234 (10 days, constant).

Periodate Uptake of PII.—Product PII (*ca.* 0·4 g.) was dissolved in water (50 c.c.), and sodium metaperiodate (0·4M.; 25 c.c.) added. Portions (5 c.c.) were withdrawn at intervals, and the periodate content was determined by the arsenite method, with the following results, expressed in mols. of periodate consumed per g.: 0·00312 (10 minutes); 0·00535 (15 minutes); 0·00638 (1 day); 0·00674 (3 days, constant).

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KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, November 9th*, 1949.]

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102. *The Structure of Peach Gum. Part I. The Sugars produced on Hydrolysis of the Gum.*

By J. K. N. JONES.

Peach gum on hydrolysis yields a mixture of D-galactose (5 parts), L-arabinose (6 parts), D-xylose (2 parts), rhamnose (*ca.* 2%), and D-glucuronic acid (1 part). The rate of hydrolysis indicates that the arabinose residues are in the furanose form; the other sugars are probably present in the pyranose form. Graded hydrolysis of the gum gives an aldobiuronic acid identified as 6-D-glucuronosido-D-galactose. Oxidation of the gum with periodic acid yields approximately two mols. of formic acid per repeating unit of equivalent weight 2040. Eight sugar residues are oxidised, of which four are arabinose, two are xylose and two are galactose.

SAMPLES of peach gum (*Prunus persica* L.) were kindly supplied from Piedmont, Italy, by Professor A. Nasini of the University of Turin, and from Bristol by Mr. R. Stitch. Examination of the physical constants of fractions of the gum indicated that it was essentially homogeneous, but it may be a mixture not separable by the methods in general use. Analysis of the sugars produced on hydrolysis of the fractions, by the use of partition chromatography (Flood, Hirst, and Jones, *J.*, 1948, 1679; Hirst and Jones, *J.*, 1949, 1659), showed that the ratio of sugars was D-galactose (5 parts), L-arabinose (6 parts), D-xylose (2 parts), and D-glucuronic acid (1 part; by difference) per equivalent weight of 2040. L-Rhamnose (*ca.* 2%) was also present. The identity

of the sugars was confirmed by graded hydrolysis of the gum. The rate of hydrolysis of the sugars, estimated by chromatographic analysis on paper, showed that L-arabinose was hydrolysed very rapidly, indicating that it is combined in the furanose form in the gum (cf. damson gum; Hirst and Jones, *J.*, 1946, 506). The D-xylose was hydrolysed rather more slowly than the arabinose, but faster than the D-galactose, which is very probably in the pyranose form. From the products of hydrolysis of the gum, pure crystalline specimens of L-arabinose, D-galactose, D-xylose, and L-rhamnose were isolated. Oxidation of the gum with potassium periodate solution led to the consumption of ten moles of periodate and the formation of approximately two moles of formic acid per equivalent of gum (2040). During this oxidation all the xylose and approximately two-thirds (4 moles) of the arabinose and two-fifths (2 moles) of the galactose are destroyed. These results follow from a quantitative analysis of the sugars present in the oxidised gum by paper partition chromatography. Some of the L-arabofuranose residues must therefore be linked through $C_{(2)}$ and/or $C_{(3)}$, because only thus will the α-glycol group [·CH(OH)·CH(OH)·] be absent in the molecule. The formic acid may have arisen from the oxidation of a D-xylopyranose, a D-galactopyranose, or a uronic acid end group. If the D-xylose was an end group, then galactopyranose residues containing 1 : 2- or 1 : 4-glycosidic linkages were present in the gum. If the galactose residues occupy terminal positions, then xylose residues substituted on $C_{(2)}$ or $C_{(4)}$ only must be present in the gum molecule.

Methylation of the barium salt of the aldobiuronic acid fraction, obtained by graded hydrolysis of the polysaccharide, yielded a non-reducing methylated aldobiuronic acid which was built up of D-glucuronic acid linked through $C_{(4)}$ of a D-galactose residue, since on hydrolysis the methylated acid gave equimolecular proportions of 2 : 3 : 4-trimethyl D-glucuronic acid (I) and 2 : 3 : 4-trimethyl D-galactose (II). The former was identified as the crystalline methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, and the identity of (II) was confirmed from its rate of movement on the paper chromatogram and by the formation of its characteristic anilide. The aldobiuronic acid is therefore composed of the same sugar residues as are the aldobiuronic acids present in arabic acid and egg plum gum.

Experimental.

The crude samples of gum consisted of a mixture of large and small nodules admixed with bark and organic debris. The gum was essentially homogeneous since nodules gave, after purification, substantially identical constants. The gum was fractionated by extracting separate nodules successively with (*a*) cold water, yielding a cold-water fraction, and (*b*) hot N-sodium hydroxide to give an alkali-soluble fraction. The insoluble residue consisted of bark and inorganic material. The fractions were purified by precipitation from aqueous solution with glacial acetic acid (twice) (Bell and Young, *Biochem. J.*, 1934, **28**, 882). This procedure removed practically all the ash and colouring matter. The gum was finally precipitated from aqueous solution by addition of methanol in order to remove acetic acid. It was thus obtained as a white powder, initially freely soluble in water, but gradually becoming insoluble. Drying in a partial vacuum rapidly caused the gum to become insoluble in water. The cold-water-soluble fraction had $[\alpha]_D^{20}$ −46° (*c*, 0·23 as the sodium salt in water) (Found : equiv., 2300; sulphated ash, 0·4%). The gum soluble in hot sodium hydroxide had $[\alpha]_D^{20}$ −47° (*c*, 0·22 as the sodium salt in water) (Found : equiv., 2200; sulphated ash, 0·3%). Samples of gum from Turin and from Bristol were not distinguishable by physical properties or chemical reactions.

A sample of each of these fractions was hydrolysed on the boiling water-bath with N-sulphuric acid for 5 hours. The cooled solution was neutralised with barium carbonate and filtered, and the filtrate examined on the paper chromatogram; galactose, arabinose, and xylose were detected in each case. Rhamnose was not detected until a later stage (see below).

Quantitative Analysis of the Sugars produced on Hydrolysis of the Gum.—Peach gum (cold-water-soluble; 100·4 mg.) was hydrolysed with N-sulphuric acid (5 c.c.) in a sealed tube in a boiling water-bath for 12 hours. The cooled tube was opened and its contents were added to a solution of ribose (41·6 mg.); acids (including uronic acids) were then removed with Amberlite Resin IR4B, and the filtered solution was concentrated to about 2 c.c. Portions (0·001 ml.) of the solution were then placed on the starting line of a sheet paper chromatogram, an Agla micrometer syringe being used, and the sugars were separated and isolated by the procedure of Flood, Hirst, and Jones (*J.*, 1948, 1679) as modified by Hirst and Jones (*J.*, 1949, 1659) (Found : galactose, 0·93; arabinose, 0·93; xylose, 0·34; ribose, 0·90 mg.; whence the percentage of galactose is 38·6 calc. as $C_6H_{10}O_5$, and that of arabinose 37·6 and of xylose 13·8 calc. as $C_5H_8O_4$). A polysaccharide of equiv. 2040 and containing five galactose residues, six arabinose residues, two xylose residues, and one uronic acid residue per average repeating unit requires : galactose, 39·6 (calc. as $C_6H_{10}O_5$); arabinose, 28·8; xylose, 12·9% (calc. as $C_5H_8O_4$). Peach gum (soluble in sodium

hydroxide) on hydrolysis and analysis, by the method detailed above, gave a mixture of galactose, arabinose, and xylose [Found: galactose, 40·2 (calc. as $C_6H_{12}O_6$); arabinose, 38·4; xylose 13·6% (calc. as $C_5H_{10}O_5$)]. Owing to the small amount present, rhamnose was not detected in these analyses.

Oxidation of Peach Gum with Potassium Periodate Solution.—The gum (547 mg. of neutral sodium salt) was dissolved in water (50 c.c.) containing potassium chloride (5 g.), sodium metaperiodate solution (50 c.c.; 0·25M.) added, and the whole shaken in the dark and in an air-tight vessel. After various time intervals, portions (25 c.c.) of the solution were withdrawn, ethylene glycol (excess) was added, and the formic acid titrated with 0·01N-sodium hydroxide, methyl-red being used as indicator [Found: 12·7 c.c. (190 hours); 12·5 c.c. (220 and 260 hours)]. This corresponds to the production of one mol. of formic acid per 1100 g. of gum, or approx. two mols. per equivalent of 2040.

The gum (516 mg.), under conditions of oxidation similar to those described above, consumed sodium periodate (4·9 c.c.; M.), whence 1 l. of M-periodate is equivalent to 211 g. of gum. It follows that approx. ten mols. of periodate are consumed per 2040 g. of gum.

Determination of the Sugars produced on Hydrolysis of the Oxidised Gum.—The gum (0·50 g.) was oxidised with potassium periodate as described above. Ethylene glycol was added to the solution after 200 hours, and the solution dialysed against distilled water until iodate and chloride ions could no longer be detected in the solution. The oxidised product (0·3 g.) was isolated by concentrating the dialysed solution to *ca.* 10 c.c. and precipitating it with methanol. The product, a pale yellow powder, was dried in a partial vacuum at 100°.

The oxidised polysaccharide (104·9 mg.) was hydrolysed by heating it with sulphuric acid (2N.; 5 c.c.) in a sealed tube in a boiling water-bath for 7 hours. The tube was cooled and the contents washed into a solution of ribose (89·3 mg.) in water. The solution was neutralised with Amberlite Resin IR4B and filtered. The filtrate was concentrated to *ca.* 1 c.c., and portions of the solution (0·001 ml.) were placed on the starting line of a sheet paper chromatogram. After separation and isolation the sugars were determined as before [Found: galactose, (*a*) 1·51, (*b*) 1·50; arabinose, (*a*) 0·57, (*b*) 0·61; ribose, (*a*) 4·35, (*b*) 4·45 mg.]. These figures correspond to the presence of the following percentage of sugars, calculated as $C_6H_{10}O_5$ and $C_5H_8O_4$, respectively: galactose, (*a*) 26·6, (*b*) 25·8; arabinose, (*a*) 10·0, (*b*) 10·4. No xylose could be detected.

Hydrolysis of Ash-free Peach Gum.—The gum (1·0 g.) was dissolved in 0·5N-sulphuric acid (25 c.c.) containing ribose (0·198 g.). The solution was heated in a closed vessel on a boiling water-bath, and at intervals samples were withdrawn and analysed [Found (reducing sugar calculated as hexose): 874 mg. (1 hour); 969 mg. (2 hours); 1·269 mg. (5 hours and 9 hours)].

Portions of the solution were withdrawn at intervals, cooled, neutralised with barium carbonate, and filtered, and the filtrate concentrated. The residual solution of sugars were analysed by the method of sheet paper chromatography [Found (percentage of sugars calc. as $C_6H_{10}O_5$ and $C_5H_8O_4$, respectively): galactose, 6·8; arabinose, 35; xylose, 8 (1 hour); galactose, 27·0; arabinose, 37·0; xylose, 13·3 (4 hours); galactose, 38·8; arabinose, 37·0; xylose, 12·8 (9 hours)]. Rhamnose was not detected in this experiment.

Autohydrolysis of the Gum.—The ash-free gum (10·52 g.) was dissolved in water (100 c.c.), and the thick brown solution heated on the steam-bath for 66 hours. At intervals, samples were withdrawn and analysed. It was not possible to follow changes in optical rotation owing to the darkness of the solution. Analysis on the paper chromatogram showed that arabinose was the first reducing sugar to appear in solution and that, after 41 hours, arabinose, xylose, and three other sugars, possibly disaccharides (their rate of movement on the paper chromatogram was about that of maltose), were present in the solution. After 52 hours, galactose, arabinose, and xylose could be detected. At this stage, the solution contained 5·4 g. of reducing sugars (calc. as hexose). This figure remained unaltered on heating of the solution for a further 14 hours.

The cooled solution was neutralised with barium hydroxide solution and filtered. The filtrate was concentrated to *ca.* 100 c.c. and poured into methanol (1 l.). The precipitated barium salts were redissolved in water and reprecipitated in methanol to remove reducing sugars, yielding a product (*A*, 2·75 g.) containing no free galactose, arabinose, or xylose (paper chromatogram). The methanolic solution on concentration gave a syrup which was exhaustively extracted with boiling methanol, yielding an alcohol-insoluble residue (*B*; 1·7 g.) and soluble sugars (*C*; 7·5 g.) obtained on removal of the solvent.

Fraction (*C*) crystallised on trituration with methanol. The crystals (3·66 g.) were filtered off and identified as L-arabinose, $[\alpha]_D^{20}$ 105° (in water), m. p. 160°. These crystals contained traces of xylose only as impurity (paper chromatogram). The non-crystalline residue was analysed on the paper chromatogram [Found: galactose, 1·27; arabinose, 0·75; xylose, 0·66 mg.; whence the weights of galactose, arabinose, and xylose present in the syrup (3·84 g.) were 1·81, 1·07, and 0·95 g., respectively]. The presence of these sugars was confirmed by the isolation of L-arabinose benzoylhydrazone, m. p. 186°, D-galactose phenylmethylhydrazone, m. p. and mixed m. p. 186°, and dibenzylidene D-xylose dimethyl acetal, m. p. 210°, not depressed on admixture with an authentic specimen. L-Rhamnose was not detected until later (see below).

The syrupy sugars (3·0 g.) from fraction (*C*) were separated on a column of cellulose by the method of Hough, Jones, and Wadman (*J.*, 1949, 2511), using *n*-butanol saturated with water as eluent. Examination of the eluate showed that the first tubes contained pure L-rhamnose, which was isolated as the crystalline hydrate (52 mg.) after recrystallisation from acetone–methanol, m. p. and mixed m. p. 100°, $[\alpha]_D$ +9° (*c*, 1·1 in water). The next few tubes contained D-xylose, which was obtained crystalline on concentration of the solvent. After recrystallisation, the product had m. p. 146° and $[\alpha]_D$ +18° (in water). Thereafter arabinose and galactose were eluted from the column but were not further examined. The residual sugars on the column were then eluted with water, the eluate was concentrated, and the residual syrupy sugars (0·52 g.) separated by the filter-paper strip method of Flood, Hirst, and Jones (*loc. cit.*), yielding the following fractions: (*a*) arabinose, (*b*) galactose, (*c*), (*d*), and (*e*) sugars moving at a rate corresponding closely to that of a disaccharide. Fractions (*a*) and (*b*) were not further examined. Fraction (*e*), which had moved very slowly indeed, was a barium salt and was discarded. Fractions (*c*) and (*d*) on hydrolysis yielded galactose, identified by its rate of movement on the chromatogram.

Fraction (*B*) (1·7 g.) was hydrolysed with 0·5N-sulphuric acid (30 c.c.) on the boiling water-bath : $[\alpha]_D^{20}$ rose to +47° (*c*, 3·4 in 0·5N-sulphuric acid ; constant value, 6 hours). The cooled solution was neutralised with barium carbonate and filtered. The filtrate was concentrated, and the syrupy residue extracted exhaustively with methanol, leaving an insoluble barium salt (0·8 g.). The methanol extract contained galactose (0·82 g.), arabinose (0·07 g.), and xylose (0·04 g.), determined by analysis on the paper chromatogram. D-Galactose was further identified by the isolation of the crystalline sugar (0·6 g.), m. p. 165°, $[\alpha]_D^{20}$ +82° (in water). The insoluble residue of barium salt (0·6 g.) was added to the barium salt obtained from fraction (*A*) (see below).

Fraction (*A*) (2·03 g.) was hydrolysed with boiling 0·1N-sulphuric acid (75 c.c.) for 12 hours : $[\alpha]_D$ rose from +29° to +47°. The cooled solution was neutralised with barium hydroxide solution and filtered, the filtrate concentrated to dryness, and the residue exhaustively extracted with methanol, leaving a barium salt (1·58 g.). Concentration of the methanolic extract gave crystalline D-galactose (0·46 g.), $[\alpha]_D^{20}$ +80°, m. p. 165°. This sample of sugar contained traces of arabinose and xylose (paper chromatogram).

Identification of Uronic Acid Fraction.—The barium salts (1 g.) from fraction (*A*) (above) were heated with sulphuric acid (2N. ; 25 c.c.) for 15 hours on the boiling water-bath to hydrolyse any remaining oligosaccharide. The cooled solution was then neutralised (a small quantity of the syrup was examined on the paper chromatogram and spots corresponding to the presence of glucurone and glucuronic acid were detected), and the sugars were converted into their methyl ethers by reaction first with methyl sulphate and sodium hydroxide until the solution was non-reducing to Fehling's reagents, and then by the addition of 30% sodium hydroxide and methyl sulphate with stirring. After completion of the addition of the reagents, the solution was boiled to destroy sodium methyl sulphate, cooled, extracted with chloroform, acidified, and again extracted with chloroform. Concentration of the latter chloroform extracts yielded trimethyl methyl-D-glucuronoside (0·42 g.) as a syrup (Found : OMe, 49·0% ; equiv., 254. Calc. for $C_{10}H_{18}O_7$: OMe, 49·6% ; equiv., 250). The D-glucuronoside (0·4 g.) was hydrolysed with N-hydrochloric acid on the boiling water-bath for 5 hours, the solution cooled, and bromine water added. When the solution no longer reduced Fehling's solution (5 days) it was aerated to remove bromine, neutralised with silver carbonate, filtered before and after the passage of hydrogen sulphide, and then concentrated to the syrupy 2 : 3 : 4-trimethyl D-glucosaccharic acid. This product was esterified by boiling it with methanolic hydrogen chloride, and the solution was then neutralised with silver carbonate and filtered. Concentration of the filtrate yielded the methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, m. p. and mixed m. p. 111°.

Isolation of a crystalline acid derivative. The residual barium salts (1·15 g.) from fractions (*A*) and (*B*) were methylated with methyl sulphate and sodium hydroxide by the procedure described above. After completion of the methylation, the solution was cooled, acidified with dilute sulphuric acid, and extracted with chloroform. Concentration of the extracts left a syrup (0·8 g.) which was methylated with Purdie's reagents and then distilled. Two fractions and a still residue were obtained : Fraction (1) (0·11 g.), b. p. 130°/0·05 mm., n_D^{18} 1·4484 (Found : OMe, 50·0%) ; this fraction on hydrolysis gave 2 : 3 : 4-trimethyl D-glucuronic acid, identified by its rate of movement on the chromatogram and by its conversion into the methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, m. p. 111°. Fraction (2) (0·23 g.), b. p. 200—230°/0·05 mm., n_D^{20} 1·4662 (Found : OMe, 51% ; equiv., 450). Still residue (0·42 g.) (Found : OMe, 40·3%). Fraction (2) (0·20 g.) was hydrolysed with 2N-hydrochloric acid (25 c.c.) for 15 hours. It was not possible to follow any change in optical rotation owing to darkening of the solution. The solution was neutralised with silver carbonate and filtered, and the filtrate treated with hydrogen sulphide and again filtered. The filtrate was concentrated to 10 c.c. and then neutralised with barium carbonate and filtered. Concentration of the filtrate left a glass which was exhaustively extracted with ether, leaving the barium salt of 2 : 3 : 4-trimethyl D-glucuronic acid, identified as the methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, m. p. and mixed m. p. 111°. The ethereal extract contained 2 : 3 : 4-trimethyl D-galactose, since a small quantity of the syrup remaining after removal of the solvent moved at the same rate as this compound on the paper chromatogram (Brown, Hirst, Hough, Jones, and Wadman, *Nature*, 1948, **161**, 720). This was confirmed by converting the syrup (0·08 g. ; $[\alpha]_D^{20}$ +87° (*c*, 0·8 in water)) into the characteristic anilide, m. p. 169°, not depressed on admixture with an authentic sample.

THE UNIVERSITY, BRISTOL. [*Received, November 10th*, 1949.]

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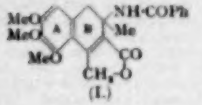
103. *Colchicine and Related Compounds. Part X.*

By J. W. COOK, T. Y. JOHNSTON, and J. D. LOUDON.

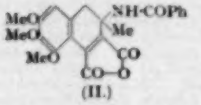
6 : 7 : 8-*Trimethoxy-3-methylnaphthalene-1* : 2-*dicarboxylic acid anhydride* (VII) has been obtained by dehydrogenation of the 3 : 4-*dihydronaphthalene* derivative (VI) which, in turn, has been synthesised from *iso*lemicine and chloromaleic anhydride. *N*-Benzoylcolchinic anhydride, formulated by Windaus as (II), does not behave as a dihydronaphthalene derivative since it has now been deaminated to *deaminocolchinic anhydride* which (*a*) is isomeric, and not identical, with 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride (VII), and (*b*) has olefinic properties as shown by its susceptibility to hydrogenation with a palladium catalyst. Deaminocolchicide also has olefinic properties. Oxidation of colchiceine and of *N*-acetylcolchinol to the same product, namely, *N-acetylcolchinic anhydride*, indicates that the size of ring D is the same in the colchinic acid as in the colchinol series of colchicine degradation products.

ACCORDING to Windaus (*Annalen*, 1924, **439**, 59) hydronaphthalene derivatives are produced when *N*-benzoyltrimethylcolchicinic acid is oxidised with cold alkaline potassium per-

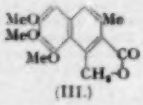
manganate. The two main products, namely, *N*-benzoylcolchide and *N*-benzoylcolchinic anhydride, were formulated as (I) and (II), respectively, although minor modification, particularly in the structure (I), was not excluded. This interpretation accounted for the known facts and contributed to the conclusion that ring B of colchicine is six-membered. It has since been established, however, that in another series of degradation products ring B occurs as a seven-membered ring (Barton, Cook, and Loudon, Part V, *J.*, 1945, 176; Buchanan, Cook, Loudon, and MacMillan, *Nature*, 1948, **162**, 692), and in consequence re-examination of the supposed hydronaphthalene structures becomes desirable. It is consistent with the dihydronaphthalene structure (I) that *N*-benzoylcolchide eliminates benzamide during hydrolysis or sublimation (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat. Kl., *A*, 1911, 2 Abh.). The deaminocolchide so produced was regarded as the "trimethoxyhomonaphthide" (III), and it might be expected on this basis that the corresponding acid anhydride (VII) would be formed either by oxidation of deaminocolchide or by deamination of *N*-benzoylcolchinic anhydride. Accordingly, the *compound* of structure (VII) has been synthesised for reference purposes.



(I.)



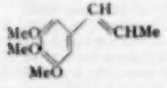
(II.)



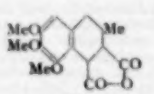
(III.)

Hudson and Robinson (*J.*, 1941, 715) recorded successful condensations of the Diels–Alder type between β-alkylated styrenes and either maleic anhydride or ethyl acetylenedicarboxylate. More recently Synerholm (*J. Amer. Chem. Soc.*, 1945, **67**, 345) reported good results by use of chloromaleic anhydride, which is satisfactorily prepared from chlorofumaric acid (Perkin, *J.*, 1888, **53**, 695) by Walden's method (*Ber.*, 1897, **30**, 2885; cf. von Auwers and Harres, *ibid.*, 1929, **62**, 1686). The diene component for our synthetic work, namely, 3 : 4 : 5-trimethoxypropenylbenzene (IV), is already known as *iso*elemicine and was prepared by Semmler (*Ber.*, 1908, **41**, 2186), who obtained it through isomerisation of elemicine, the naturally occurring 3 : 4 : 5-trimethoxyallylbenzene. Although elemicine may be prepared from the allyl ether of 2 : 6-dimethoxyphenol (Hahn and Wassmuth, *Ber.*, 1934, **67**, 696; Pearl, *J. Amer. Chem. Soc.*, 1948, **70**, 1746) and might therefore be used as a source of *iso*elemicine, we have prepared the latter by dehydrating the carbinol which is produced from 3 : 4 : 5-trimethoxybenzaldehyde and ethylmagnesium bromide.

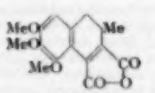
A preliminary experiment showed that, under the conditions used by Hudson and Robinson, condensation between *iso*elemicine and maleic anhydride was accompanied by much polymerisation although the formation of (V) was indicated by isolation of the corresponding dibasic *acid* from which the *anhydride* itself was obtained on sublimation. The condensation of *iso*elemicine with chloromaleic anhydride was then examined in various solvents, and the *anhydride* (VI) was ultimately obtained in 45—50% yield by heating the reactants in xylene with the addition of quinol to inhibit polymerisation (cf. Norton, *Chem. Reviews*, 1942, **31**, 319). It might be expected from the work of Bergmann (*J. Amer. Chem. Soc.*, 1942, **64**, 176; *J. Org. Chem.*, 1943, **8**, 183) that condensation to the dihydronaphthalene derivative (VI) when conducted in nitrobenzene would be followed by dehydrogenation to the naphthalene derivative (VII), but in practice under these conditions dehydrogenation was not observed. On the other hand, when (VI) was submitted to slow sublimation there occurred disproportionation of hydrogen with formation of (VII) and (V), the latter again being isolated as the dibasic acid ;



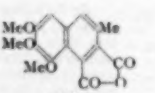
(IV.)



(V.)



(VI.)



(VII.)

moreover, dehydrogenation of (VI) to (VII) was readily effected by heating with palladium in a current of carbon dioxide. In contrast to the tetrahydronaphthalene (V), which is colourless, the anhydrides (VI) and (VII) are yellow and orange respectively. All three anhydrides dissolved in alkali to give colourless solutions from which on acidification the colourless dibasic *acids* corresponding to (V) and (VI) were respectively obtained, but the acid corresponding to

(VII) rapidly reverted to the anhydride and was not analysed. The facility with which anhydrides are obtained from naphthalene-1 : 2-dicarboxylic acids has already been noted by Hudson and Robinson (*loc. cit.*) and our observations are consistent with increasing ease of formation in the order (V) < (VI) < (VII).

As expected, the naphthalene derivative (VII) was unaffected by exposure to hydrogenation conditions with a palladium catalyst, but under the same conditions an abnormal behaviour was shown by the dihydronaphthalene derivative (VI). This compound, dissolved in acetic acid, rapidly absorbed one mole of hydrogen and then, unexpectedly, slowly absorbed a second mole, the initial yellow colour of the solution being discharged only during the latter stage of absorption. Subsequent isolation of 6 : 7 : 8-trimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-dicarboxylic acid in considerable quantity showed that (V) is a major product of the reaction but the nature of the side reaction remains undetermined. The same dicarboxylic acid was formed by reduction of (VI) with zinc and acetic acid.

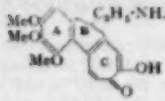
Part of the colchicine required for degradative work was purchased from Messrs. Ransom (Hitchin, Herts.) as the concentrates of an alcohol extract of *Colchicum* seeds, and the alkaloid was isolated by the procedure of Chemnitius (*J. pr. Chem.*, 1928, **118**, 29) combined with chromatographic purification (cf. Ashley and Harris, *J.*, 1944, 677). The derived *N*-benzoyltrimethylcolchicinic acid was prepared as described by Windaus (*loc. cit.*, 1911) but attempted repetition of his oxidation experiments on this compound gave much less satisfactory results. Although *N*-benzoylcolchide and *N*-benzoylcolchinic anhydride were both identified, the smallness of the yields severely restricted the scope of further degradative work. Moreover, even under the experimental conditions which are stated (Windaus, *loc. cit.*, 1911) to afford *N*-benzoylcolchide, the anhydride appeared to be the predominant product. In addition to benzamide, benzoic acid, and probably *N*-benzoylcolchinic acid, which were incidentally isolated, two unidentified oxidation products were obtained in small quantities and have not yet been examined in detail.

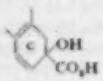
Thermal decomposition of *N*-benzoylcolchinic anhydride takes a different course from that described by Windaus for *N*-benzoylcolchide. The latter compound yields benzamide and deaminocolchide whereas it is now found that the anhydride yields benzamide only in traces; the main product of the decomposition is a neutral nitrogenous *substance* to which the provisional formula, $C_{31}H_{19}O_4N$, is assigned pending fuller investigation when an adequate supply of material becomes available. However, when heated with phosphoric oxide in xylene (cf. Cook and Graham, Part III, *J.*, 1944, 322; Cook, Dickson, Ellis, and Loudon, Part VII, *J.*, 1949, 1074), *N*-benzoylcolchinic anhydride yielded *deaminocolchinic anhydride*, and this compound proved to be quite distinct from the synthetic 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride (VII).

When subjected to quantitative micro-hydrogenation over a palladium catalyst neither *N*-benzoylcolchide nor *N*-benzoylcolchinic anhydride absorbed hydrogen, although the latter compound is already known (Windaus, *loc. cit.*, 1911) to contain one ethylenic linkage which can be reduced by means of zinc and acetic acid. It may be recalled that in both colchicine and colchiceine, apart from the aromatic ring, there is one double bond which resists catalytic hydrogenation (Bursian, *Ber.*, 1938, **71**, 245) and a similar resistant double bond therefore appears to be maintained in the above degradation products. On the other hand, both deaminocolchide—prepared as described by Windaus (*loc. cit.*, 1911) by hydrolysis of *N*-benzoylcolchide—and deaminocolchinic anhydride undergo hydrogenation with palladium as catalyst, absorbing one and two moles of hydrogen, respectively. The difference in the extent of hydrogenation is remarkable but, although it was ascertained that in each case a crystalline product results, shortage of material prevented further inquiry. None the less, the fact of hydrogenation under these conditions strongly indicates that the double bond which is produced in each case by deamination does not form part of an aromatic ring. In the same connection it may be noted that *N*-benzoylcolchide is not completely deaminated by six hours' heating with concentrated hydrochloric acid in ethanol. The amine, colchide, is a part-product of the reaction and consequently survives conditions which, if it were correctly formulated as (I; H for COPh), should readily transform it into the aromatic structure (III). These objections to a (hydro)naphthalene structure in the present compounds find their counterparts in objections which led to revision of the (hydro)phenanthrene structure in colchinol derivatives (Cohen, Cook, and Roe, Part I, *J.*, 1940, 194; Part V, *loc. cit.*). They suggest that the size of ring B may not in fact be different in the two sets of colchicine degradation products.

In the series of reactions by which colchiceine is converted into the dibenz*cyclo*heptatriene (XI) there appear to be only two opportunities for rearrangement in the carbon structure of

ring B. These opportunities occur (i) during the change from colchiceine to *N*-acetylcolchinol (X; R = H), whereby ring C becomes aromatic, and (ii) in the deamination of *N*-acetylcolchinol


(VIII.)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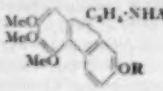
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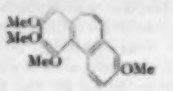
(XI.)

methyl ether (X; R = Me) ⟶ (XI). The available evidence makes it rather unlikely that the size of ring B is affected at either stage. In particular, as discussed in Parts I, V, and VII, it is highly improbable that the deamination step involves expansion of a six- to a seven-membered ring. The process by which ring C becomes phenolic is more obscure, but in terms of Dewar's tropolone formula (VIII) for colchiceine (*Nature*, **1945**, **155**, 141) the change may proceed through (IX) and ultimately to (X; R = H) without involving ring B. This change, however, is still without analogy among other tropolone compounds, where aromatisation generally leads to a derivative of benzoic acid rather than of phenol. It is of considerable interest, therefore, that by means of alkaline potassium permanganate we have now been able to oxidise both colchiceine and *N*-acetylcolchinol to the same product, namely, *N*-acetylcolchinic anhydride which Windaus (*loc. cit.*, 1911) had already obtained from the first-named source, although he does not record analytical figures. The possibility of molecular rearrangement during the course of these oxidations cannot be excluded. Indeed, the preparation of *N*-acetylcolchinol from colchiceine involves oxidation—by hypoiodite, followed by reduction of the intermediate *N*-acetyliodocolchinol (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat.Kl., *A*, **1914**, 18 Abh.), or by hydrogen peroxide (Šantzavý, *Chem. Listy*, **1949**, **43**, 156)—in an alkaline medium and the course of oxidation with permanganate may well be similar. Even so, unless invalidated by the *renewed* incidence of rearrangement, the conclusion follows that the carbon structure of ring B is the same in colchinol as in colchinic anhydride.

In general, therefore, the results described serve to unify the problems relating to the structure of ring B in the two main series of the alkaloid's degradation products. Questions of detailed structure in individual compounds remain unsettled and to these we hope to devote our attention.

Experimental.

3 : 4 : 5-*Trimethoxyphenylethylcarbinol*.—A solution of 3 : 4 : 5-trimethoxybenzaldehyde (20·3 g.) in anhydrous ether (400 c.c.) was added with cooling and stirring to the Grignard reagent prepared from ethyl bromide (20 g.), magnesium turnings (4·5 g.), and ether (40 c.c.). After 16 hours at 0°, the mixture was treated with a saturated aqueous solution of ammonium chloride. The ethereal layer, combined with ethereal washings of the aqueous layer, was washed with water, concentrated, and shaken with aqueous sodium hydrogen sulphite which removed a little unchanged aldehyde. The carbinol, obtained by evaporating the solvent from the washed and dried ethereal solution, was a viscous, pale yellow liquid (23·15 g.).

iso*Elemicine*.—The carbinol, to which a crystal of iodine had been added, was heated under distillation conditions at diminished pressure and with a tower of sodium hydroxide pellets in the circuit to trap uncondensed vapours. Vigorous effervescence occurred at relatively low temperatures and *iso*elemicine (85—87%) was collected up to 150°/0·4 mm., was redistilled, showing b. p. 110—115°/0·4 mm. (Found : C, 68·9; H, 7·7. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·7%), and identified as the dibromide, m. p. 92—93° (Found : C, 39·5; H, 4·5. Calc. for $C_{12}H_{16}O_3Br_2$: C, 39·1; H, 4·35%) (Semmler, *loc. cit.*, gives m. p. 89—90°). Prepared in this way, the product was only slightly yellow and was accompanied by a small higher-boiling residue which afforded a second fraction, b. p. 204°/0·4 mm., as a yellow resin with violet fluorescence.

Less satisfactory yields of *iso*elemicine were obtained by heating the carbinol for 30 minutes at 160° with (*a*) dehydrated alum and some crystals of quinol (yield 46%) (cf. Barnett and Lawrence, *J.*, 1935, 1104) or (*b*) potassium hydrogen sulphate (yield 63%), whilst (*c*) with phosphoric oxide in boiling xylene or (*d*) with thionyl chloride in cold dry pyridine (cf. Ellis and Petrow, *J.*, 1939, 1081) the yields were very poor. In all of these cases the ether-soluble product, after distillation of *iso*elemicine, gave a high-boiling resin which in case (*b*) was heated for 1 hour at 140° with anhydrous oxalic acid and, after recovery in ether and washing with alkali, afforded a viscous fluorescent distillate, b. p. 200°/0·1 mm., which crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 187° (Found : C, 69·1; H, 7·6%), and was probably a dimer.

6 : 7 : 8-*Trimethoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-1 : 2-*dicarboxylic Acid and its Anhydride* (V).—A solution of *iso*elemicine (0·328 g.) and maleic anhydride (0·773 g.) in xylene (5 c.c.) was boiled under reflux for 8 hours and then left at room temperature for 2 days. Xylene and maleic anhydride were distilled off (up to 70°/0·6 mm.), and the residue, treated with ether, afforded an amorphous solid which was again heated (at 130°/0·1 mm.) to remove volatile material. Thereafter crystallisation from acetic acid gave the *acid* as colourless plates, initially melting at 197—198° but reverting on storage to m. p. 181—182° (Found : C, 59·2; H, 6·3. $C_{16}H_{20}O_7$ requires C, 59·3; H,

6·2%); when melted at atmospheric pressure and then sublimed at 200—210°/0·1 mm., the acid yielded the *anhydride*, micro-m. p. 93° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 63·0; H, 5·4. $C_{14}H_{16}O_4$ requires C, 62·75; H, 5·9%).

6 : 7 : 8-*Trimethoxy*-3-*methyl*-3 : 4-*dihydronaphthalene*-1 : 2-*dicarboxylic Acid and its Anhydride* (VI).—(*a*) A solution of *iso*lemicine (0·753 g.) and chloromaleic anhydride (2·4 g.) in dry nitrobenzene (8 c.c.) was heated under reflux for 1½ hours. Nitrobenzene and chloromaleic anhydride were distilled off (up to 61°/1 mm.) and the residue was treated with ether, an insoluble, dark product being discarded. Concentration of the solution gave the anhydride (0·29 g., 26%), m. p. 132—135° [from ether–light petroleum (b. p. 40—60°)].

(*b*) A mixture of *iso*lemicine (6·02 g.), chloromaleic anhydride (6 g.), xylene (18 c.c.), and a few crystals of quinol was heated under reflux for 23 hours. From the clear solution, filtered if necessary, there were distilled off (i) xylene under water-pump pressure and (ii) a mixture of chloromaleic anhydride and *iso*lemicine (up to b. p. 140°/0·3 mm.) from which the latter (0·218 g.) was recovered by treatment with alkali and redistillation. The non-volatile residue when treated with ether afforded yellow needles of the *anhydride* (4·346 g.), m. p. 134—135° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 63·1; H, 5·45. $C_{14}H_{14}O_6$ requires C, 63·2; H, 5·3%), and on concentration of the ethereal mother-liquor there first separated crystals of chlorofumaric acid (0·5 g.), m. p. and mixed m. p. 190—191°, and the remainder on extraction with alkali and acidification yielded an impure sample (0·126 g.) of the dibasic *acid* corresponding to (VI). The same acid was prepared by warming (VI) with 10% aqueous sodium hydroxide, followed by acidification of the cooled solution; it formed colourless crystals, m. p. 146—147° (effervescence) (from acetic acid), and appeared to retain solvent in the crystal (Found: C, 56·7; H, 5·6. $C_{14}H_{16}O_7,C_2H_4O_2$ requires C, 56·5; H, 5·8%), but gave the correct analytical figures—and same m. p. behaviour—after crystallisation from water (Found: C, 59·8; H, 5·5. $C_{14}H_{16}O_7$ requires C, 59·6; H, 5·6%).

When rapidly sublimed (½ hour) at 200°/0·1 mm., the acid yielded the anhydride (VI), m. p. and mixed m. p. 135°, but on slower sublimation at 190—200°/18 mm. the later fractions of the sublimate gave the dehydrogenated anhydride (VII), m. p. and mixed m. p. 190—192° (from acetic acid), whilst the mother-liquor on storage slowly deposited colourless plates of 6 : 7 : 8-trimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-dicarboxylic acid, m. p. and mixed m. p. 208° and 208—210°, respectively (effervescence). The same acid was obtained when a solution of the anhydride (VI) in acetic acid was heated for 3 hours at 100° with an excess of zinc dust, the product being recovered from the filtered solution and purified by passage in benzene through a column of silica gel.

6 : 7 : 8-*Trimethoxy*-3-*methylnaphthalene*-1 : 2-*dicarboxylic Anhydride* (VII).—The anhydride (VI) (0·71 g.), mixed with palladium (0·19 g.), was heated in a slow stream of dry carbon dioxide at 230—240° for 1½ hours. The product, which had partly sublimed, was recovered in ether and formed yellow needles, m. p. 194—194·5°, from ether (Found: C, 63·8; H, 4·65. $C_{14}H_{14}O_6$ requires C, 63·6; H, 4·6%). The anhydride was regenerated by dissolution in alkali and acidification.

Isolation of Colchicine.—A concentrated ethanolic extract of *Colchicum* seeds (333 g.; from Messrs. Ransom), diluted with water (450 c.c.), was heated with paraffin wax (75 g.), and the liquid mixture, after vigorous stirring, was cooled, the solidified wax layer was lifted off, and the aqueous layer was re-treated with fresh wax (75 g.). The wax layers were extracted with boiling water (3 × 100 c.c.), and the total aqueous solution was mixed with "Hyflo Supercel" (100 g.). After filtration, using a pre-coat of "Hyflo", the filter-bed was well washed. The combined filtrates were exhausted with acid-free chloroform (12 × 200 c.c.) which, after being dried (K_2CO_3) and concentrated, afforded a brownish-yellow syrup. A solution of the syrup in chloroform (150 c.c.) was passed through a column of alumina (25 × 3·5 cm.; from B.D.H.; saturated with benzene) which retained much adsorbed material in several distinct zones (still under examination), and the colchicine was eluted by continued passage of chloroform until the eluate, initially yellow, became colourless and left no residue on evaporation. The recovered syrup was dissolved in ethanol which was then distilled off, the process being repeated thrice to ensure removal of chloroform. The final residue crystallised from ethyl acetate in fine colourless needles of m. p. 148—150° raised by renewed chromatography to m. p. 155°; $[\alpha]_D^{17}$ −119·9°, $[\alpha]_{5461}^{17}$ −167·8° (*c* = 0·878 in chloroform).

N-Benzoylcolchicinic Anhydride.—A solution of *N*-benzoyltrimethylcolchicinic acid (3·24 g.) in 3% aqueous potassium hydroxide (32 c.c.) was treated (20 minutes) under cooling with 4% potassium permanganate (208 c.c.). After 12 hours the mixture was acidified with sulphuric acid and clarified by a stream of sulphur dioxide. A chloroform extract yielded an orange syrup which was dissolved in ethyl acetate, the solution was shaken with 2% aqueous sodium carbonate (which extracted acidic material including some benzoic acid), washed, and concentrated. When rubbed with benzene the residue afforded a brown solid (*A*) (0·477 g.), m. p. 193° (from benzene), and the benzene mother-liquor when passed through a short column of silica gel and eluted with benzene yielded (*a*) in the first colourless eluate, a few crystals of benzamide, m. p. and mixed m. p. 127°, and (*b*), in the yellow eluate, the anhydride, m. p. 201—202° (Windaus records m. p. 207°). Solid (*A*) when similarly purified afforded the anhydride as rectangular yellow plates, m. p. 201—202° (Found: C, 65·3; H, 4·8; N, 3·5. Calc. for $C_{33}H_{31}O_7N$: C, 65·25; H, 5·0; N, 3·3%). Recrystallisation from chloroform–ethyl acetate (1 : 1) gave the compound as flat rectangular plates, m. p. 211—212°.

In course of exploratory experiments on the purification of solid (*A*), combined benzene mother-liquors were passed through a column of alumina (B.D.H.) on which, however, adsorption was rather strong. Elution with benzene gave (i) a faintly yellow eluate which on concentration afforded stout, almost colourless crystals of a neutral *substance* (*B*), m. p. 164° (from benzene), recrystallising as colourless hexagonal plates, micro-m. p. 157° (from the same solvent) (Found: C, 69·7; H, 5·6; N, 4·2. $C_{11}H_{17}O_5N$ requires C, 69·4; H, 4·7; N, 3·9%. $C_{11}H_{19}O_5N$ requires C, 69·05; H, 5·2; N, 3·6%), and (ii) a yellow eluate, from which on concentration some benzamide crystallised, m. p. and mixed m. p. 127·5°.

Sublimation of N-Benzoylcolchicinic Anhydride.—When the anhydride (0·09 g.) was heated at 220—230°/18 mm. in a sublimation apparatus the melt bubbled vigorously for about 30 minutes, and the

slight yellow sublimate at this stage crystallised from benzene as a mixture of radiating yellow needles of unchanged anhydride (probably present as the result of splashing) and a few colourless rectangular plates of benzamide, micro-m. p. 122° raised to 124—126° by admixture with an authentic specimen. The subsequent orange-red sublimate, collected during 90 minutes while the temperature was gradually raised to 250—260°/18 mm. (leaving a non-volatile, uncrystallisable residue), afforded small colourless prisms, which had micro-m. p. 159—160° after several crystallisations from benzene (Found: C, 69·3; H, 5·25; N, 4·0; OMe, 25·0. $C_{21}H_{19}O_5N$ requires C, 69·05; H, 5·2; N, 3·85; OMe, 25·5%).

Evaporation of the first benzene mother-liquor from this *substance* afforded a semi-crystalline gum from which there was obtained a mixture of colourless prisms, micro-m. p. 170—171°, and yellow needles, micro-m. p. 196—206° (effervescence) (from aqueous acetic acid). These are probably secondary products and await further investigation.

Deaminocolchinic Anhydride.—A hot solution of *N*-benzoylcolchinic anhydride (90 mg.) in purified xylene (8 c.c.) was treated with phosphoric oxide (250 mg.), and the whole was heated under reflux for 20 minutes. The hot solution was decanted from the red gelatinous phosphoric residues which were then washed (*a*) with fresh boiling xylene (2 × 6 c.c.) and (*b*) with boiling chloroform (3 × 8 c.c.). The combined and cooled xylene solution was again decanted from a slight deposit of gelatinous substance and was then concentrated at 18 mm. The cooled concentrates deposited masses of golden-yellow rectangular plates or prisms of micro-m. p. 170—171° from benzene–light petroleum (b. p. 60—80°) (Found: C, 63·8; H, 4·7. $C_{14}H_{14}O_4$ requires C, 63·6; H, 4·6%). A further small quantity of the same *substance* was recovered from the chloroform washings (*b*). It was only slowly affected by cold, but dissolved in hot, dilute alkali giving a colourless solution.

Hydrogenation.—The product (5·36 mg.) in acetic acid (4 c.c.) and in presence of palladium black absorbed 0·90 c.c. of hydrogen at 20°/760 mm., corresponding to 2·1 double bonds. There was recovered from the still faintly yellow solution a gum which crystallised from benzene–light petroleum (b. p. 60—80°) as needles of micro-m. p. 108—110°.

N-*Benzoylcolchide.*—A solution of *N*-benzoyltrimethylcolchicinic acid (7 g.) in 2% potassium hydroxide (70 c.c.) was treated at 0—3° with 4% potassium permanganate (350 c.c.), and after 4 hours the manganese dioxide was filtered off and washed (i) with boiling water, the aqueous filtrates being combined, and (ii) with boiling ethanol, the (moist) solution on concentration affording a gummy solid in aqueous suspension. Separate extraction of the filtrate (i) and suspension (ii) with chloroform gave, after drying and recovery, brown amorphous solids (0·168 g. and 0·454 g., respectively), whilst, after concentration of the filtrate (i) to small bulk under reduced pressure and in a stream of carbon dioxide, renewed extraction afforded a further quantity (0·917 g.) of a similar solid. Attempts to purify the various fractions by selective extraction with ethyl acetate (cf. Windaus, *loc. cit.*) failed, and the combined material was dissolved in much benzene, transferred to a column of silica gel, and eluted with benzene. Concentration of the faintly yellow eluate afforded a mixture of colourless plates and needles, which was separated by fractional crystallisation from benzene–methanol into (i) benzamide, m. p. and mixed m. p. 127°, and (ii) *N*-benzoylcolchide (0·143 g.), micro-m. p. 236° (Windaus gives m. p. 239°). Final elution of the column with methanol gave a brown residue (1·237 g.) recoverable from the eluate, but attempts to purify this material or to obtain from it crystalline hydrolysis products were unsuccessful.

The manganese dioxide was added to the aqueous concentrates, and the acidified mixture was clarified by a stream of sulphur dioxide before being extracted with chloroform. The extract was washed with 2% sodium carbonate (which removed resinous acidic material; 1·805 g.), dried, and concentrated. A solution of the residue (2·3 g.) in benzene was separated on silica gel into an upper bright yellow section (brown in ultra-violet light) and a lower colourless section (yellow in ultra-violet light). Separate elution with benzene, followed by concentration, gave: (i) colourless rectangular plates (0·040 g.) probably of *N*-benzoylcolchinic acid (arising from incidental hydrolysis) since they melted and effervesced at 182° with formation of the anhydride and were also formed from the anhydride by dissolving the latter in alkali and acidifying the solution; (ii) yellow rectangular plates (1·432 g.) of *N*-benzoylcolchinic anhydride, m. p. 194—195°; and (iii) unidentified stout prisms of micro-m. p. 201°, which were soluble in hot alkali.

Deaminocolchide and Colchide Picrate.—A solution of *N*-benzoylcolchide (0·078 g.) in 95% ethanol (3·5 c.c.) and concentrated hydrochloric acid (3 c.c.) was heated under reflux for 6 hours. The ethanol was distilled off and water (3 c.c.) was added. After 24 hours the precipitate was collected and shaken with ether, unchanged *N*-benzoylcolchide (0·027 g.) remaining undissolved (and being re-treated). Deaminocolchide (0·014 g.), micro-m. p. 130° (from aqueous ethanol) (Windaus gives m. p. 138°), was recovered from the ethereal solution and was slightly augmented by material recovered from an alkali-washed ethereal extract of the aqueous mother-liquor. Concentration of the aqueous mother-liquor and addition of aqueous picric acid gave colchide picrate, micro-m. p. 160—161° (Windaus gives m. p. 165°). Anomalous hydrolysis results were obtained in one experiment where, instead of deaminocolchide, colourless crystals of micro-m. p. 153—155° (from aqueous ethanol) were isolated. This substance was distinct from the oxidation product, micro-m. p. 157°, of *N*-benzoyltrimethylcolchicinic acid and it was not again encountered.

Hydrogenation.—A solution of deaminocolchide (3·59 mg.) in acetic acid (4 c.c.) in presence of palladium black absorbed 0·310 c.c. of hydrogen at 18·8°/751 mm., corresponding to 1·03 double bonds. The product, recovered from the acetic acid solution, formed colourless prisms of micro-m. p. 79—81° from aqueous ethanol.

N-*Acetylcolchinic Anhydride.*—(*a*) A solution of colchiceine (2 g.) in 3% potassium hydroxide (25 c.c.) was treated during 9 hours at 0° with 4% aqueous potassium permanganate (150 c.c.). After a further 12 hours the mixture was acidified, sulphur dioxide was passed in to dissolve the manganese dioxide, and the whole was extracted with chloroform. The brown gum recovered from the chloroform was extracted with benzene, the solution was passed through a column of silica gel, and the yellow section of the resulting chromatogram was eluted with benzene. After renewed chromatography, concentration of the yellow eluate afforded a minute quantity of colourless nodules, micro-m. p. 200° (not further

examined), mixed with a larger proportion of yellow needle clusters. The latter afforded *N*-acetylcolchinic anhydride, micro-m. p. 184—185° (from ether) (Found: C, 60·15; H, 4·9. Calc. for $C_{18}H_{21}O_7N$: C, 59·9; H, 5·3%) [Windaus, *loc. cit.*, 1911, records (macro-) m. p. 201°].

(*b*) A solution of *N*-acetylcolchinol (0·4 g.) in 3% potassium hydroxide (6 c.c.) was titrated at 20° in the course of 48 hours with 4% potassium permanganate (23·6 c.c.). Discharge of the permanganate colour, at first rapid, was later very slow. The manganese dioxide was filtered off and washed with hot water and then with boiling ethanol, the washings being concentrated and added to the main filtrate, which was then acidified and extracted with chloroform. The recovered brown gum was dissolved in benzene–chloroform (1 : 1), and the solution was passed through a short column of silica gel, from which the yellow eluate on evaporation afforded clusters of yellow needles, micro-m. p. and mixed m. p. with the product from (*a*) 184—185°.

We are glad to acknowledge our indebtedness to Messrs. Imperial Chemical Industries Limited (Dyestuffs Division) for making it possible for one of us (T. Y. J.) to take part in this investigation, to the Royal Society and the Chemical Society for grants for the purchase of colchicine, and to Messrs. Roche Products, Limited, for the gift of a sample of colchicine. Microanalyses were carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, November 18th*, 1949.]

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104. *The Low-temperature Polymerisation of* isoButene. *Part II.**

By P. H. PLESCH.

The polymerisation of isobutene in hexane solution by titanium tetrachloride with water and trichloroacetic acid as co-catalysts was investigated at temperatures between −90° and 0°, by an adiabatic technique. The kinetic data, which are of a preliminary nature, show that the reaction is of the first order with respect to the co-catalyst. There are indications that the activation energy of chain initiation is probably less than 4 kcals./mole and that the activation energy of chain termination may be as high as 10 kcals./mole. This is interpreted in terms of the rearrangement of the ion pair at the growing end of the polymer chain when termination takes place. Analytical data indicate that the co-catalyst may be built into the end of the chain at termination. The polarised-molecule theory is shown to be inapplicable to this system, and the carbonium ion theory is developed. The S-shaped reaction curves obtained under certain conditions are explained in terms of a slow build-up of the concentration of growing chains.

THE polymerisation of *iso*butene at low temperatures by Friedel–Crafts catalysts has been the subject of numerous investigations, which have been reviewed recently (Heiligmann, *J. Polymer. Sci.*, 1949, **4**, 183; Plesch, *Research*, 1949, **2**, 267; *Proc. Roy. Dublin Soc.*, Symposium on Friedel–Crafts Polymerisations, in the press). In this laboratory we have mainly used titanium tetrachloride as catalyst (Plesch, Polanyi, and Skinner, *J.*, 1947, 257, who quote also Seymour, Thesis, Manchester, 1943; A. G. Evans *et al.*, *Nature*, 1946, **157**, 102; Plesch, *Nature*, 1947, **160**, 868) and the outcome of the early work with this halide and of parallel work with boron trifluoride (Evans, *loc. cit.*; A. G. Evans, Meadows, and Polanyi, *Nature*, 1947, **160**, 869; Evans and Polanyi, *J.*, 1947, 252; Evans and Meadows, *J. Polymer Sci.*, 1949, **4**, 359) was the conclusion that in these reactions a third component, called the co-catalyst, was essential. It was found that atmospheric moisture acted as such a co-catalyst. The reactions by means of which this effect was investigated at low temperatures were carried out adiabatically in hexane solution and were followed by recording the temperature rise caused by the heat of polymerisation.

When the reaction was initiated by passing a brisk stream of moist air through a non-reacting solution of *iso*butene and titanium tetrachloride in hexane, the reaction curves (time–temperature plots) were always S-shaped (Plesch, Polanyi, and Skinner, *loc. cit.*, Figs. 3 and 4). Frequently it was found that a given dose of moist air would induce a reaction which would cease before all the monomer had been consumed. In such cases a second dose of moist air would induce a further reaction (*loc. cit.*, Fig. 4). Although the detailed course of the reactions was not reproducible, an examination of the temperature dependence of the initial and maximum rate of reaction showed a certain regularity, as can be seen from Figs. 1 and 2 below. These results suggest that the rate of the polymerisation co-catalysed by water vapour has a positive temperature coefficient. This is the direct opposite of what had been found in our rough preliminary experiments (*loc. cit.*) and by other workers (*e.g.*, Thomas *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 276; Waterman *et al.*, *Rec. Trav. chim.*, 1934, **53**, 699). An explanation of this will be suggested in the Discussion below.

* Part I, *J.*, 1947, 257.

Although the discovery of the rôle of water in these polymerisations had made clear at least one of the possible causes of the irreproducibility, which seemed to characterise the polymerisation of *iso*butene, the deliberate use of water vapour as co-catalyst had not lead to any appreciable degree of reproducibility in these reactions. The reasons for this are not difficult to find.

Water vapour introduced into a hydrocarbon solution at a temperature far below 0° must form a dispersion of ice and therefore its action could not be envisaged as anything but heterogeneous. This view was supported by the milky appearance of the final polymer solution. Even if the water had been initially in a molecularly disperse form in the reaction mixture it must be presumed that the titanium tetrachloride–water complex which is postulated as the real initiator of the reaction (Plesch, Polanyi, and Skinner, *loc. cit.*) would not be soluble in the mixture of *iso*butene and hexane and would tend to form aggregates. Thus the rate and extent of reaction would depend on the size and number of these aggregates and on the rate at which they settled out on the walls and fittings of the reaction vessel.

FIG. 1.

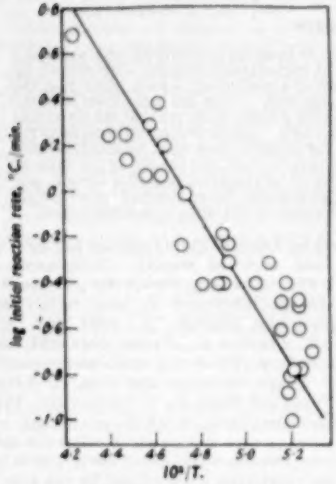


FIG. 2.

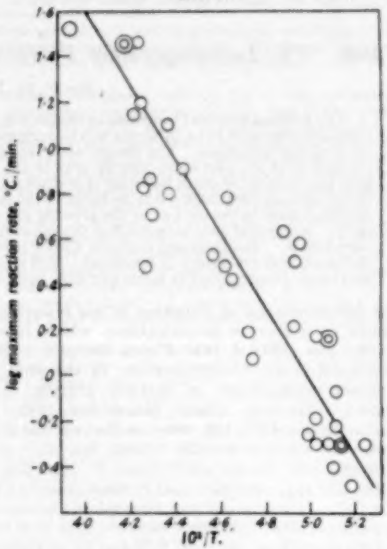


FIG. 1.—*Adiabatic polymerisation of isobutene (2·5 moles/l.) by* $TiCl_4$ *(4·8 × 10⁻⁵ mole/l.), co-catalysed by water vapour. Initial rate as a function of temperature.*
FIG. 2.—*Maximum rate as a function of temperature. Otherwise as for Fig.* 1.

For these reasons we attempted to find a co-catalyst which would make it possible to carry out the reaction under homogeneous conditions. We required a co-catalyst which would be soluble in a hydrocarbon medium and whose complexes with titanium tetrachloride would also be soluble in such a medium. It was evident that no inorganic substance was likely to fulfil both these conditions. Investigations in these laboratories running parallel to the work reported here had shown that acetic acid (Evans, Meadows, and Polanyi, *loc. cit.*) and *tert.*-butanol (Evans and Polanyi, *loc. cit.*) are capable of acting as co-catalysts to boron trifluoride in the polymerisation of gaseous *iso*butene at room temperature, but neither of these substances was found to be effective as co-catalyst to titanium tetrachloride in the low-temperature polymerisation of *iso*butene (Plesch, *Nature*, 1947, **160**, 868). On the contrary, they were found to act as inhibitors to this reaction. Diethyl ether and ethanol have been reported previously (Plesch, Polanyi, and Skinner, *loc. cit.*) to have a similar inhibiting effect.

The Present Investigation.

Qualitative Results. The Survey of Co-catalysts.—The qualitative results of the search for co-catalysts other than water are presented in Table I. According to our views on the nature of this polymerisation, a substance, in order to act as co-catalyst, must be capable of forming with the catalyst a complex which is a sufficiently strong acid to donate a proton to the monomer, thus converting it into a carbonium ion. It is well known that concentrated sulphuric acid will polymerise *iso*butene to a product of low molecular weight at room temperature, but we found that it would not do so at low temperatures. We thought that possibly sulphuric acid might form with the titanium tetrachloride a complex acid strong enough to initiate polymerisation at low temperatures, though of course such a complex could not be expected to be soluble in hexane. Experiment showed that concentrated sulphuric acid did indeed act as a very potent co-catalyst at −80°. Since the effect might have been due to the water contained in the sulphuric acid, 20% oleum which could not contain any water was tried and was found to be as effective as sulphuric acid. The reactions co-catalysed by sulphuric acid were very violent and virtually complete, and the product was of relatively low molecular weight, probably not above 20,000.

Table I.

T_r	*iso*Butene concn., mols./l.	$TiCl_4$ concn., 10^{-3} mols./l.	Test substance, *X*.	Concn. of *X*, millimols./l.	Effect.
−87°	2	4·8	Conc. H_2SO_4	50	Vigorous polymn.
−86	2	0	" "	50	No polymn.
−79	2	4·8	20% oleum	50	Vigorous polymn.
−68	2	4·8	"	50	"
−79	2	0	"	50	No "
−25 to −120	0·62 to 2·5	0·2 to 5	$CCl_3{\cdot}CO_2H$ in hexane	0·25 to 6·5	Polymn.
−75	1·25	4·8	$CHCl_2{\cdot}CO_2H$ in hexane	1·9 9·5 [c]	Slight indication of polymn.; poisoning [b]
−75	1·25	4·8	$CH_2Cl{\cdot}CO_2H$ in hexane	>1·0 [d]	No polymn.; poisoning
−62	2·5	2·4	$CH_3{\cdot}CO_2H$ in hexane	0·85	No polymn.; poisoning
−60	2·5	2·4		0·85	
−76	2·5	2·4		8·5	
+20	2·5	2·4		8·5	

[a] T_r is the temperature of the reaction mixture when *X* was added. [b] "Poisoning" means that the addition of trichloroacetic acid or water vapour to a reaction mixture to which the reagent *X* had been added previously, caused no reaction, or only at a rate much smaller than that in the absence of *X*. [c] Two separate additions of this acid to the same reaction mixture were made. [d] An emulsion of the (liquid) acid in hexane was used.

Since it was thought that other strong acids might act in a similar manner, trichloroacetic acid was tried, and was indeed found to possess a strong co-catalytic activity. Its acid strength in water is of the same order as that of sulphuric acid and it has the advantage for the present purpose of being appreciably soluble in hexane even at −80°. The complexes which it forms with titanium tetrachloride also appear to be soluble in hexane. The main part of this paper is devoted to the results of polymerisation studies carried out with this co-catalyst.

Experimental.

Purification of Reagents.—Hexane. Commercial hexane was purified by standard methods; it was distilled from phosphoric oxide through a 3-ft. point column, and the fraction distilling between 67·5° and 68·5° was collected. It was stored over phosphoric oxide until introduced into the reservoir attached to the polymerisation apparatus.

Titanium tetrachloride. The commercial product was distilled in a stream of dry air until the intensity of the pale yellow colour could not be reduced by further fractionations. A weighed quantity was dissolved in the calculated quantity of pure dry hexane in the absence of atmospheric moisture, to give a 0·6M-solution (approx. 12% w/v). It was prepared in batches of about 200 ml. and stored in a reservoir connected to the polymerisation apparatus. The solution was almost colourless, clear, and free from deposit even after several months' storage. The colour of the titanium tetrachloride was caused by traces of iron and chromium.

isoButene. This was a much appreciated gift from Messrs. I.C.I. (Billingham) Ltd., and was stated to be 99% pure. Before use it was distilled *in vacuo* from about −80° to liquid-air temperature until the liquid was perfectly clear and free from white flocks. For the experiments an amount of *iso*butene approximately equal to that required was collected in a roughly graduated trap, and the exact amount determined by weighing.

Trichloroacetic acid. The commercial, pure but deliquescent product was crystallised 4 times from hexane, and then dissolved in hexane to give an approx. N/10-solution. This was stored over phosphoric oxide and its strength was determined by titration. Such solutions could be thus stored for several weeks without undergoing change in concentration.

Apparatus and Technique.—The apparatus and technique used in the present series of polymerisation experiments were essentially the same as those previously described (Plesch, Polanyi, and Skinner, *loc. cit.*) which had been used for studying the co-catalytic effect of water vapour. The quantities of hexane, *iso*butene, and catalyst solution were always so adjusted that the volume of the whole batch was 200 ml. at room temperature.

The reaction was started by adding to the non-reacting solution of *iso*butene and titanium chloride in hexane a measured quantity of the co-catalyst solution from a pipette through an opening in the stopper of the reaction vessel. It was ascertained by control experiments that the amount of atmospheric moisture admitted to the reaction vessel during this addition of the co-catalyst was insufficient to cause measurable reaction.

The progress of the reaction was observed by noting the temperature of the reaction mixture on a pentane thermometer at definite time intervals. Since the polymerisation of *iso*butene is exothermic by more than 10 kcals./mole, the temperature changes accompanying this reaction provide an accurate and sensitive means of observation. For instance, the complete polymerisation of 7 g. of *iso*butene (0·125 mole) in 190 ml. of hexane gave a temperature rise of 14° in our apparatus.

At the end of the reaction 2—3 ml. of 90% ethanol were added to the polymer solution. This removed the catalyst by precipitating it as a pale yellow oil, leaving a clear and colourless solution of poly*iso*butene in hexane.

Measurement of Molecular Weight.—The mean molecular weight of the poly*iso*butene specimens obtained in the course of this work was calculated from the intrinsic viscosities of their solutions in hexane, by means of the formula (Houwink, *J. pr. Chem.*, 1940, **157**, 15) $[\eta] = KM^a$, where $[\eta]$ is the intrinsic viscosity, M is the mean molecular weight, and K and a are constants.

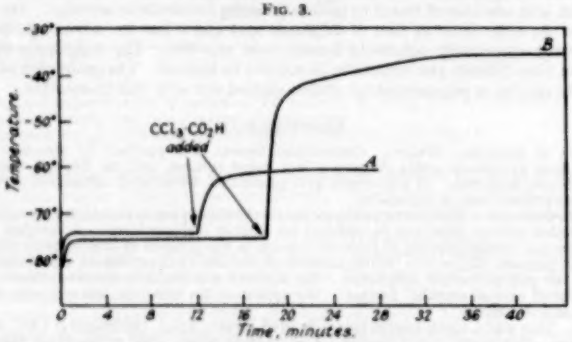
The intrinsic viscosity of the unfractionated polymer was determined as follows: After reaction a small portion of the mixture discharged from the reaction vessel was made up into an approx. 1% w/v solution in hexane, and this was diluted, *e.g.*, to $\frac{1}{2}$, $\frac{1}{3}$, and $\frac{1}{4}$. The flow times of not less than three such solutions were measured in the usual manner in a B.S.S. 188 No. 1 U-tube viscometer at 25°, and from it and the flow time of the pure solvent the specific viscosity $\eta_{sp.}$ was calculated. After the timing, the content of the viscometer was weighed in a tared weighing-bottle, dried to constant weight (16 hours at 90—110°), and re-weighed. Hence the concentration c of the polymer was found. The plot of $\log(\eta_{sp.}/c)$ against c, extrapolated to $c = 0$, gave the intrinsic viscosity $[\eta]$, from which the molecular weight was calculated by the above formula, with $K = 3{\cdot}6 \times 10^{-4}$ and $a = 0{\cdot}64$. As these constants had been obtained by Flory (*J. Amer. Chem. Soc.*, 1943, **65**, 372) for solutions of poly*iso*butene in di-*iso*butene it was ascertained by experiment that there was no significant difference between the intrinsic viscosities of poly*iso*butene in this solvent and in hexane.

Duplicate determinations of the molecular weights obtained in this way agree to within 5%, but their relation to the true weight-average and number-average molecular weights is somewhat doubtful, as the measurements were carried out on unfractionated specimens, whereas the constants in the formula had been obtained from measurements on carefully fractionated polymer samples.

Polymerisation with Trichloroacetic Acid as Co-catalyst.

General.—The polymerisation of *iso*butene by titanium tetrachloride and trichloroacetic acid has been studied under a variety of conditions. It was found that the polymerised solutions were always much less opaque than those which had been produced with water vapour as co-

Fig. 3.

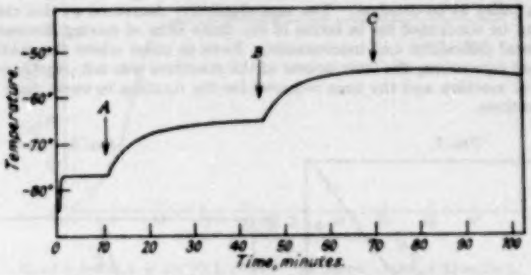


Adiabatic polymerisation of isobutene. *Typical time–temperature curves. Catalyst:* $TiCl_4$ (48 *millimoles/l.*). *Concn. of* isobutene: A 2·5, B 0·62 *mole/l. Concn. of* CCl_3CO_2H: A 1·65, B 3·3 *millimoles/l. Catalyst added at time* = 0.

catalyst, and the orange-red crystalline sediment, which had always been present when water was used, was absent from the solutions polymerised with trichloroacetic acid.

Whereas the curves showing the progress of reaction with time (time–temperature curves) obtained with water-vapour co-catalysis were always S-shaped, the rate of the reactions induced by trichloroacetic acid decreased monotonically from the start, provided that the molar ratio

FIG. 4.



Adiabatic polymerisation of isobutene in hexane solution by $TiCl_4$ *and* $CCl_3{\cdot}CO_2H$. *Concn. of isobutene,* 10% (*v/v*, i.e., ~0·25 *mole*/200 *c.c.*), *and of* $TiCl_4$, 1% (*v/v*, i.e., 9·6 × 10^{-3} *mole*/200 *c.c.*). *The* $TiCl_4$ *was added at* t = 0. *The quantities of trichloroacetic acid added were at* A 6·6 × 10^{-5} *mole*, B 3·3 × 10^{-4} *mole, and at* C 6·6 × 10^{-4} *mole.*

FIG. 5.

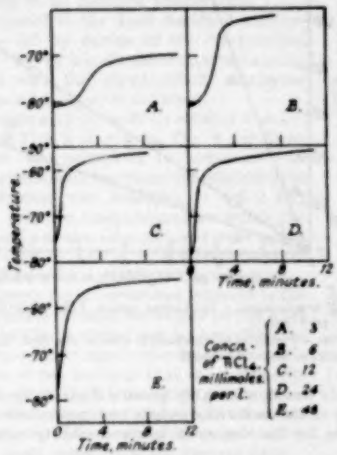


FIG. 6.

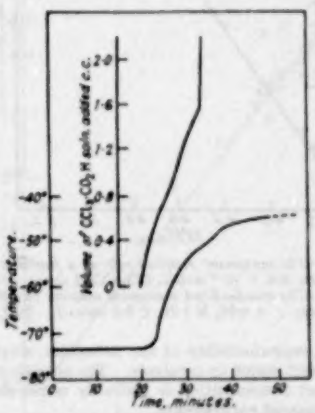


FIG. 5.—*The effect of varying the catalyst : co-catalyst ratio. Concn. of isobutene* 1·25 *mole/l. Concn. of* $CCl_3{\cdot}CO_2H$ 3·3 *millimoles/l.*

FIG. 6.—*Slow addition of a solution of* $CCl_3{\cdot}CO_2H$ (1·2 × 10^{-3} *mole/c.c.*) *in hexane to* 200 *c.c. of isobutene solution* (1·25 *moles/l.*) *containing* 4·8 × 10^{-3} *mole/l. of* $TiCl_4$.

titanium tetrachloride/trichloroacetic acid was greater than about 4 (for starting temperatures near −80°) (Figs. 3 and 4). For reactions in which this ratio was less than 4, the time–temperature curves became the more pronouncedly S-shaped, the lower the value of this ratio (see Fig. 5).

The shape of the time–temperature curve is also influenced by the rate at which the co-catalyst is added to the reaction mixture. By adding it at a small and constant rate, S-curves can be produced even in the presence of excess of catalyst (see Fig. 6).

When the co-catalyst is added at the usual very high rate, *e.g.*, 1 ml. in less than 5 seconds in the presence of excess of catalyst, the reaction rate is greatest at the very start of the reaction. Although temperature readings were taken every 15 seconds, the finite time required for the co-catalyst to enter the mixture—even when this is well stirred, as it always was—introduced a considerable error into the determination of the maximum reaction rate when this was given by the temperature rise during the first 15 seconds from the addition of the co-catalyst.

The reproducibility of the maximum reaction rate was much greater than in the experiments carried out with water as co-catalyst. The reproducibility decreased as this rate increased, a feature which can be accounted for in terms of the finite time of mixing discussed above, and of the experimental difficulties and inaccuracies. Even in cases where the maximum (initial) rates were in close agreement, the later course of the reactions was not exactly reproducible so that the extent of reaction and the time required for the reaction to cease were variable for a given set of conditions.

FIG. 7.

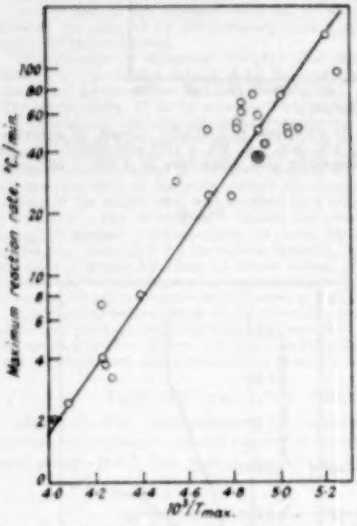


FIG. 8.

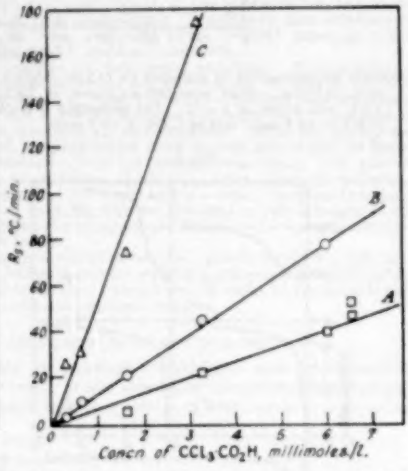


FIG. 7.—*The maximum reaction rate as a function of temperature.* isoButene *concn.* 1·25 *moles/l.*, $TiCl_4$ *concn.* $4·8 \times 10^{-3}$ *mole/l.* CCl_3CO_2H *concn.* 6×10^{-3} *mole/l.*

FIG. 8.—*The standardised maximum reaction rate* R, *as a function of co-catalyst concn. for three* isobutene *concns.:* A 0·62, B 1·25, C 2·5 *moles/l.* $TiCl_4$ *concn.* 48 *millimoles/l.*

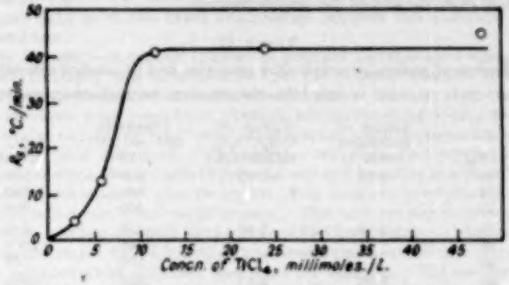
The reproducibility of the molecular weights was considerably greater than in the experiments with water co-catalysts. The sensitivity of the molecular weight to temperature and to monomer concentration is probably responsible for the degree of irreproducibility remaining in the present experiments.

The kinetic results to be presented below must be regarded as preliminary for the reason that they were obtained from adiabatic experiments. None the less they provide some new information about the mechanism of this polymerisation. In the present investigations we have determined the influence of the concentrations of isobutene, titanium tetrachloride, and trichloroacetic acid, and of the starting temperature of the reaction, on the maximum reaction rate and the molecular weight.

Variation of the Maximum Reaction Rate with Temperature.—The logarithm of the maximum reaction rate was plotted against the reciprocal of the absolute temperature $T_{max.}$ at which the maximum rate occurred (Fig. 7). In very fast reactions this was not very well defined. For all the experiments represented in Fig. 7 the isobutene concentration was 1·25 moles/l. (10% v/v)

and the catalyst (titanium tetrachloride) and co-catalyst (trichloroacetic acid) concentrations were $4{\cdot}8 \times 10^{-4}$ and 6×10^{-4} moles/l. respectively (1% and 0·5% w/v respectively). These results indicate a negative "activation energy" of about −7·5 kcals./mole for the over-all reaction.

FIG. 9.



R, *as a function of the* $TiCl_4$ *concn.* isoButene *concn.*, 1·25 *moles/l.* $CCl_3{\cdot}CO_2H$ *concn.*, $3{\cdot}3 \times 10^{-4}$ *mole/l.*

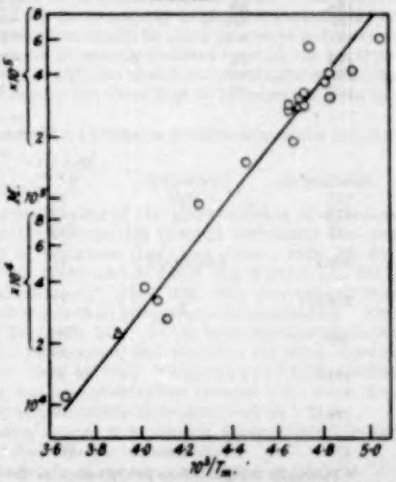
Effects of the Concentrations of the Three Reactants on the Maximum Reaction Rate.—While studying these effects it was impossible to adjust conditions in such a manner that the maximum rate always occurred at the same temperature. For this reason the observed maximum rate occurring at an absolute temperature $T_{max.}$ was adjusted to the fixed standard temperature −75° by means of the "activation energy" of −7·5 kcals./mole reported above. In this way the standardised maximum reaction rates R_s were obtained.

Variation of R, *with Co-catalyst Concentration.*—This is shown in Fig. 8 for three different concentrations of *iso*butene. In these experiments the titanium tetrachloride concentration was constant at $4{\cdot}8 \times 10^{-4}$ mole/l. and the temperatures at which the maximum reaction rate occurred were in the region −70° to −85°. R_s is seen to increase linearly with the co-catalyst concentration.

Owing to the uncertainties inherent in the experimental method the slopes of the lines shown in Fig. 8 should not be considered as more than a first approximation. The ratios of these slopes indicate that the polymerisation is probably of an order greater than unity with respect to *iso*butene, but it would not be justifiable to attempt an evaluation of the exact order from the present data.

Dependence of the Standardised Maximum Reaction Rate R_s *on the Titanium Tetrachloride Concentration.*—For constant *iso*butene and co-catalyst concentrations, this dependence is shown in Fig. 9. Beyond a certain point the rate appears to be independent of the catalyst concentration.

FIG. 10.



The mean mol. wt. of the polymer as a function of the mean absolute temperature during the reaction. iso*Butene concn.* 1·25 *moles/l.* $CCl_3{\cdot}CO_2H$ *concn.* 3·3 *millimoles/l.* $TiCl_4$ *concn.* 48 *millimoles/l.* (○), 24 *millimoles/l.* (△).

Yield of the Polymerisation.—For a fixed catalyst concentration of $4{\cdot}8 \times 10^{-4}$ mole/l. the polymerisation of a 5% v/v solution of *iso*butene goes to at least 90% completion for T_s (the starting temperature) in the region of −75°, provided that the trichloroacetic acid concentration

is greater than about $1{\cdot}2 \times 10^{-4}$ mole/l. For higher concentrations of *iso*butene the yields were not reproducible, probably in consequence of the high viscosity of these solutions.

Effect of Temperature on the Molecular Weight of the Polymer.—In Fig. 10 the logarithm of the molecular weight is plotted against the reciprocal of the mean temperature T_m during the experiment. T_m is the arithmetic mean between the starting temperature T_o and the final temperature of the reacted solution at the end of the polymerisation.

TABLE II.

The variation of molecular weight with monomer and co-catalyst concentration.

In all the experiments recorded in this table the titanium tetrachloride concentration was $4{\cdot}8 \times 10^{-3}$ mole./l.

Expt. no.	$-T_m$.	Concn. of *iso*butene, mols./l.	Concn. of $CCl_3{\cdot}CO_2H$, millimol./l.	Observed mol. wt. (M) $\times 10^{-3}$.	M_n $\times 10^{-3}$.	Mean M_n $\times 10^{-3}$.
154	60°	1·25	0·66	286	950	600
158	74			250	280	
159	73			460	550	
151	70	1·25	1·65	420	640	800
152	61			325	1000	
156	58			190	750	
149	60	1·25	3·3	305	1000	840
153	61			280	880	
177	65			270	840	
181	66			310	650	
180	66			400	820	
155	58	1·25	6·6	270	1000	—
157	62			580	1600	
178	60			280	950	
166	69	0·62	1·65	430	720	—
164	68		3·3	280	500	
165	68		6·6	285	500	
167	69		6·6	240	400	
163	61	2·5	0·33	400	1250	—
161	55		1·65	280	1350	
162	56		3·3	255	960	

TABLE III.

Specimen no.	Co-catalyst	Mol. wt.[a] $\times 10^{-3}$.	Found.[b] C, %.	H, %.	Cl, %.	Calc.[c] Cl, %.
121	H_2O	20	—	—	0	0
119	,,	22	—	—	0	0
77	,,	243	85·2	14·4	0	0
206.I[e]	$CCl_3{\cdot}CO_2H$	11	—	—	1·7 2·1	1·0
206.II[f]	,,	11	—	—	0·2 0·6	1·0
189	,,	22·4 28·4[d]	—	—	0·2 0·7	0·48
194.I	,,	26	85·2 85·1	12·6 14·2	0·3	0·4
194.II	,,	26	85·3 85·3	14·0 14·2	0·3	0·4
156	,,	190	85·5	14·5	0	0·056

[a] Molecular weight before precipitation of the polymer. [b] Micro-analyses by Messrs. Weiler and Strauss, Oxford, England. [c] Assuming the presence of one trichloroacetate group per molecule. [d] Molecular weight after two precipitations. [e] Reaction mixture washed three times with distilled water, dried, and evaporated in a high vacuum. [f] Reaction mixture precipitated in methanol–acetone mixture, washed with acetone, and evaporated in a high vacuum.

Effects of the iso*Butene and Co-catalyst Concentrations on the Molecular Weight.*—Table II records results showing these effects. Since the mean temperature during the polymerisation has such a great effect on the molecular weight, the measured values of the molecular weight (M) were adjusted to the standard temperature $-75°$ by means of T_m, the mean temperature

during the reaction, and the relation between T_m and M is represented in Fig. 10. The standardised molecular weights thus obtained are designated by M_s.

It is seen from the table that M_s shows only a slight increase with the co-catalyst concentration but that it increases with the *iso*butene concentration. In view of the uncertainties involved in the calculation of the M_s values, and considering that these refer to the mean molecular weight of the end-product of the reaction, it would not be justifiable to draw any definite conclusions from these data as to the exact relationship between the molecular weight and the monomer concentration.

Analysis of the Polymer.—A certain number of polymer samples were analysed for chlorine. The main practical difficulty was to make sure that the polymer was free from trichloroacetic acid and from hydrolysis products of titanium tetrachloride.

The polymer solutions were freed from titanium tetrachloride by adding 2—3 ml. of ethanol to the solutions at the end of the reactions. This reacted with the titanium tetrachloride, and the product separated as a yellow oil. The polymer was then precipitated in a large excess of 90% ethanol and the visco-elastic mass of polymer was well kneaded in a fresh batch of ethanol. It was then dissolved in hexane to give an approx. 20% solution, precipitated again in ethanol, kneaded in ethanol, and again dissolved in hexane. The solution was then evaporated *in vacuo* at room temperature. When the bulk of the hexane had been removed, evacuation by way of a liquid-air trap was continued for 24 hours, at a pressure less than 10^{-3} mm. Hg. The colourless and transparent polymer thus obtained was used for analysis. The results of the analyses are shown in Table III. In one case (No. 194) the original polymer solution was divided into two portions, one of which (194.I) was precipitated in boiling water and the polymer so obtained dissolved in hexane and then precipitated in ethanol and thereafter treated as described. The second portion (194.II) was treated in the usual way with two ethanol precipitations. There is no difference between the chlorine contents of these two specimens. The absence of chlorine from specimens 119 and 121 which were prepared by water co-catalysis shows that where any chlorine was found in the polymers it could not have originated from end-groups derived from the catalyst. This is further supported by the absence of an incombustible residue. The absence of chlorine from the specimens 77 and 156 rules out the possibility of physical entrainment of chlorine compounds in polymer micelles, since this effect would be much greater in polymers of higher molecular weight. The precipitation process necessarily removes some of the fractions of lowest molecular weight (this is shown in specimen 189) and thus it is understandable that the measured chlorine content of the polymers is slightly less than that to be expected from the molecular weight determined before precipitation.

The data presented in Table III thus indicate that chlorine is present only in the polymer when trichloroacetic acid was used as co-catalyst.

Discussion.

The Mechanism of the Polymerisation.—The mechanism of the polymerisation of *iso*butene by Friedel-Crafts catalysts is now believed to involve reaction between carbonium ions and monomer. The original carbonium-ion theory of Whitmore (*Ind. Eng. Chem.*, 1934, **26**, 94), Hunter and Yohe (*J. Amer. Chem. Soc.*, 1933, **55**, 1248), and Brunner and Farmer (*J.*, 1937, 1039) was developed by Polanyi and his collaborators (*J.*, 1947, 252, 257) who showed that a co-catalyst, as well as the halide catalyst, was required to bring about polymerisation. This was confirmed by Norrish and Russell (*Nature*, 1947, **160**, 543). It has been shown again in the present work that a co-catalyst is essential for the reaction and therefore the older theories such as those of Price (*Annals N.Y. Acad. Sci.*, 1943, **44**, 368; "Reactions at Carbon-Carbon Double Bonds" New York, 1946) and Eyring and his collaborators (*Annals N.Y. Acad. Sci.*, 1943, **44**, 382), which ignored this, cannot apply to the systems investigated by us.

According to our present views, the initiating species is a complex between catalyst and co-catalyst, which is formed by the reaction (I) shown in the scheme below.

The complex is thought to react with a molecule of monomer according to reaction (II) in which XA^-H^+ represents the complex ion pair. This is the initiation step which involves the transfer of a proton from the catalytic complex to a molecule of monomer.

The propagation of the polymerisation is believed to take place by the combination of the carbonium ion formed in the initiating step with a molecule of the monomer, with transference of the charge to the end of the chain thus formed (Polanyi and his collaborators, *loc. cit.*). This is represented in reaction (III). In the previous attempts at formulating the propagation mechanism, the question of the fate of the anion was left open. It is clear, however, that in the system under consideration the anion cannot be separated to any considerable distance

from the carbonium ion. If one uses the method of Fuoss and Kraus (*J. Amer. Chem. Soc.*, **1933**, **55**, 1019) to calculate the degree of dissociation of the ion pair

$$\sim CH_2 \cdot (CH_3)_2 C^+ \cdot (Cl_3 C \cdot CO_2 \cdot TiCl_4)^-$$

in hexane at $-80°$, one obtains a value of the order of 10^{-m}. Therefore in the course of chain propagation the anion must remain in the vicinity of the carbonium-ion end of the growing polymer chain. A. G. Evans and Meadows (*J. Polymer Sci.*, **1949**, **4**, 359), approaching the problem in a rather different manner, reached the same conclusion. This is an additional reason why the older theories (Price, *loc. cit.*; Eyring, *loc. cit.*; Heiligmann, *J. Polymer Sci.*, **1949**, **4**, 183) which involve considerable charge separation cannot be applicable to this system.

The termination of the chains could take place by several different mechanisms : The ion pair at the growing end of the polymer chain may undergo a unimolecular rearrangement to give an ester (or alcohol if the co-catalyst is water) (Norrish and Russell, *loc. cit.*) as shown in reaction (IV*a*). In this case the halide will remain co-ordinated on to the oxygen of the terminal group. It will only be removed by treating the polymer with, *e.g.*, water which can break up the co-ordination complex. This was shown by Staudinger ("Die hochmolekularen organischen Verbindungen," Berlin, **1932**) with polystyrene prepared with stannic chloride as catalyst, and is confirmed by our observation that addition of water to a clear polymerised reaction mixture which had been freed from excess of titanium tetrachloride by the addition of alcohol produced a tenuous but quite definite white precipitate presumed to be titanium oxide.

The suggested mechanism accounts for the consumption of the co-catalyst in the course of the reaction, which is indicated by experiments such as that represented in Fig. 4 and it is supported by the analytical evidence given in Table III.

The formation of *tert.*-butyl trichloroacetate by a bimolecular reaction between monomer and the ion pair, leaving the polymer with a terminal double bond [reaction (IV*b*)], is a possibility which cannot be neglected, especially at higher temperatures. It would also account for the consumption of the co-catalyst.*

The alternative is the loss of a proton from the growing end of the polymer chain, leaving a terminal double bond. This process could take place in three different ways : (*a*) A unimolecular decomposition of the terminal ion-pair in which the catalytic complex is regenerated [reaction (V*a*)]. (*b*) A bimolecular reaction with monomer, leading to chain transfer [reaction (V*b*)]. (*c*) A bimolecular reaction with the terminal double bond of a dead polymer molecule formed by process (IV*b*), (V*a*), or (V*b*) in which the catalytic complex is regenerated as in (*a*) [reaction (V*c*)].

The complete reaction is thus represented by the scheme on following page.

If for the moment the transfer reactions (V) are neglected, the set of differential equations describing this reaction scheme with the termination mechanism (IV*a*) is as set out below.

This is analogous to the schemes used by Eley and Pepper (*Trans. Faraday Soc.*, **1947**, **43**, 112; cf. Pepper, *ibid.*, **1949**, **45**, 397, and Eley and Richards, *ibid.*, p. 425).

$$-\mathrm{d}[\mathrm{AH}]/\mathrm{d}t = k_c c[\mathrm{AH}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$-\mathrm{d}[\mathrm{CAH}]/\mathrm{d}t = -\frac{\mathrm{d}[\mathrm{AH}]}{\mathrm{d}t} - k_t m[\mathrm{CAH}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$-\mathrm{d}m/\mathrm{d}t = k_t m[\mathrm{CAH}] + k_p m\mathrm{M}^\bullet \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\mathrm{d}\mathrm{M}/\mathrm{d}t = k_t \mathrm{M}^\bullet \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\mathrm{d}\mathrm{M}^\bullet/\mathrm{d}t = k_t m[\mathrm{CAH}] - k_t \mathrm{M}^\bullet \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Where concentrations are as follows : m *iso*butene, c titanium tetrachloride, [AH] trichloroacetic acid, [CAH] initiating complex, $\mathrm{M}^\bullet$ growing polymer chain, and M dead polymer chain.

If we make the usual stationary state assumption, *i.e.*, put $\mathrm{M}^\bullet$ = constant, and also assume that k_p and k_t are independent of chain length, we get for the rate of reaction

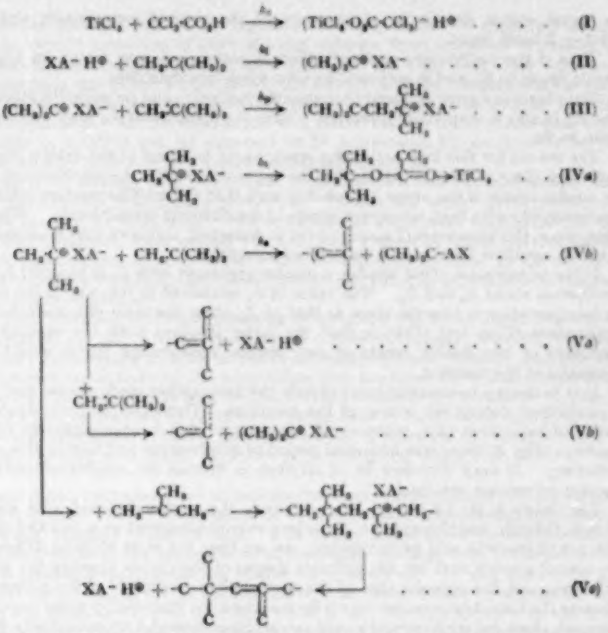
$$-\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{k_t k_p}{k_t} \cdot m^\bullet[\mathrm{CAH}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

when $k_p m/k_t \gg 1$.

If we make the plausible assumption that reaction (I) goes practically to completion in the presence of excess of titanium tetrachloride, the unknown term [CAH] can be replaced by the known co-catalyst concentration [AH].

* *iso*Butene and trichloroacetic acid react rapidly to give the *tert.*-butyl ester (Scovill, Burke, and Lankelma, *J. Amer. Chem. Soc.*, **1944**, **66**, 1039).

It is indeed found in the present work that the maximum reaction rate is proportional to the first power of the co-catalyst concentration, but the correlation cannot be regarded as definitely established until isothermal measurements are available. The order of the reaction with respect to monomer cannot be derived unambiguously from the present set of measurements, though it is probably greater than unity.



The dotted lines in this scheme indicate alternative positions for the double bond.

The molecular weight of the polymer is given by

$$M = M^0 m(k_p/k_t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where M^0 is the molecular weight of the monomer. The present data indicate that the molecular weight depends on the monomer concentration and is independent of the co-catalyst concentration; but again the data do not permit one to deduce exactly how the monomer concentration affects the molecular weight.

If termination takes place by reaction (IV*b*) the maximum reaction rate is given by

$$-\mathrm{d}m/\mathrm{d}t = k_t m[\mathrm{CAH}]$$

if $k_p/k_t \gg 2$. The molecular weight is given by

$$M = M^0 k_p/k_t$$

The facts that the observed order of the reaction rate with respect to monomer concentration is between 1 and 2, and that the molecular weight depends on a power of m rather less than 1, may indicate that both termination mechanisms (IV*a*) and (IV*b*) play a part in this reaction.

Although the present data on the concentration-dependence of the rate and molecular weight do not provide much information, the temperature dependence of these quantities yields some interesting results. Considering first the reaction with termination (IV*a*), we assume that the

number-average molecular weight of the final polymer is given by equation (7), and denote by E_i, E_p, and E_t the activation energies corresponding to the three rate constants. We then find from Figs. 7 and 10 that

$$E(\text{rate}) = E_i + E_p - E_t$$

and

$$E(\text{Mol. wt.}) = E_p - E_t$$

are equal within the limits of accuracy of the present experiments and have a value of $-7{\cdot}5 \pm 2$ kcals./mole.

Thus if the mechanism outlined above is correct we may assign an upper limit of about 4 kcals./mole to E_i, and it may well be very much less than this.

Since there is a great similarity between the initiation and propagation reactions, it is probable that E_p is also a very small quantity. Thus it appears that E_t may well be as high as 6—10 kcals./mole.

The reason for this high activation energy may be found in the drastic rearrangement which must take place in the ion pair during the termination act. In the course of chain propagation the configuration of the anion is probably such that the trichloroacetate residue is co-ordinated symmetrically with both its oxygen atoms to the titanium tetrachloride. When the termination takes place, this symmetrical arrangement is disturbed, and both ions must rearrange themselves so that a covalent bond can be formed between them.

If the termination (IV*b*) applies, a similar argument with E_s in place of E_t leads to the same conclusions about E_i and E_p. The value of E_s estimated in this way is the same as that of E_t. Its interpretation is also the same as that of E_t, since the main difference between termination mechanisms (IV*a*) and (IV*b*) is that the latter involves both the making and breaking respectively of two double bonds of very similar constitution which would hardly affect the energetics of the reaction.

It is necessary to examine more closely the assumption made above, that a stationary state is established during the course of the reactions. There can be little doubt that during the period of maximum rate, whenever it may occur, this is approximately true. But in some reactions (Fig. 5) there was an initial period of acceleration and during this, conditions are not stationary. It may therefore be of interest to discuss the conditions under which S-shaped reaction curves are obtained.

The Origin of the S-Curves.—If we compare the results obtained with water as co-catalyst (Plesch, Polanyi, and Skinner, *loc. cit.*) which were summarised on p. 543 and the results obtained with trichloroacetic acid as co-catalyst, we see that the most striking differences between the two sets of experiments are the different shapes of the curves showing the progress of reaction with time, and the opposite sign of the temperature coefficient of the polymerisation velocity. Whereas the time–temperature curves for reactions co-catalysed by water vapour were invariably S-shaped, those for trichloroacetic acid co-catalysis showed a monotonically decreasing reaction rate unless the concentration of catalyst was smaller than about four times the concentration of co-catalyst. The third condition under which S-curves are obtained is the slow addition of the co-catalyst (Fig. 6). If we ask the question: What is the feature which is common to the different circumstances which give rise to S-shaped curves?, we find that in each case there is a good reason to assume that the rate of formation of the chain-initiating species is low, so that the maximum concentration of growing polymer chains is built up slowly. This explanation of sigmoid reaction curves was previously suggested by Eley and Pepper (*loc. cit.*) for the polymerisation of n-butyl vinyl ether by stannic chloride.

A. G. Evans and Meadows (*J. Polymer Sci.*, 1949, **4**, 359) have shown that in the polymerisation of *iso*butene by boron trifluoride and acetic acid (AcOH) the complex BF_3.AcOH is very much more active than the complex $BF_3(AcOH)_2$, and that the latter may be entirely inactive. We may assume by analogy that in our system we have the equilibria

$$TiCl_4 + 2CCl_3{\cdot}CO_2H \rightleftharpoons TiCl_4{\cdot}2CCl_3{\cdot}CO_2H \quad \ldots\ldots \text{(a)}$$

$$TiCl_4{\cdot}2CCl_3{\cdot}CO_2H + TiCl_4 \rightleftharpoons 2(TiCl_4{\cdot}CCl_3{\cdot}CO_2H) \quad \ldots\ldots \text{(b)}$$

where the 1 : 1 complex is the initiating species. It is evident that, when the concentration of the acid is small compared to that of the halide, almost all the acid will be present in the form of the active complex so that the initial rate of chain initiation will be the maximum. If the concentration of acid is increased during the reaction by adding the acid slowly to the reaction mixture, the number of growing chains will increase with time and an acceleration of the reaction will be observed, as was indeed found (Fig. 6).

On the other hand, if the concentration of the catalyst is of the same order as that of the co-catalyst, an appreciable fraction of the latter will be in the form of the inactive complex. The consumption of the active complex by chain initiation will shift the equilibrium, so that more of it is formed and thus the concentration of growing chains increases with time and the reaction curve is sigmoid. Fig. 5 shows how the S-character of the reaction curves becomes more pronounced as the ratio catalyst : co-catalyst is diminished, as is to be expected from this hypothesis.

The S-shaped curves obtained with water vapour as co-catalyst can be explained on the same basis, since the rate of formation of the initiating complex from titanium tetrachloride and an ice dispersion in the circumstances of the experiment can only have been very low. Accordingly, if we conclude that in these experiments the formation of the complex was the rate-governing step, we can now explain the positive temperature coefficient of the over-all reaction rate with water as co-catalyst; for the interaction of a finely divided solid phase (ice) with titanium tetrachloride in solution can be expected to be accelerated by an increase in the temperature so that we may in fact expect a quasi-autocatalytic effect.

It might be thought, by analogy with free-radical polymerisation that the acceleration may be due to the slow consumption of inhibiting impurities. Though this would certainly enhance the effect, it cannot account for it entirely. For if impurities alone were responsible for the effect, a second reaction induced, after partial reaction, in a system in which polymerisation had ceased through consumption of co-catalyst would be expected to show no acceleration. That this is not so is shown by Plesch, Polanyi, and Skinner (*loc. cit.*, Fig. 4), the second reaction showing well-developed acceleration.

The increase in polymerisation rate with decreasing temperature which was found by previous workers (Waterman, *et al.*, *loc. cit.*; Thomas *et al.*, *loc. cit.*; Bresler, *Doklady*, 1945, **47**, [vi], 410), and in the preliminary experiments in more or less open vessels (Plesch, Polanyi, and Skinner, *loc. cit.*), can be explained tentatively by the supposition that the lower the initial temperature of the reaction mixture, the more atmospheric moisture would condense in the system, and hence that there would be a greater number of particles to participate in the heterogeneous reaction. However, the ill-defined conditions of these experiments make it pointless at present to discuss further the undoubtedly very spectacular explosive polymerisations which take place at very low temperatures.

Norrish and Russell (*loc. cit.*) attempted to explain the acceleration of ionic polymerisations in terms of the inhibition of mutual termination of carbonium and carbanion polymerisation chains by the increasing viscosity of the medium. This theory cannot apply to polymerisations in hydrocarbon media because of the impossibility of separating the ions, even if the possibility of the existence of carbanion polymerisation chains were admitted. In any case, Eley and Pepper (*loc. cit.*) have shown that in the polymerisation of n-butyl vinyl ether by stannic chloride in light petroleum the acceleration sets in before there is any marked increase in viscosity. Bresler (*loc. cit.*) also found that ionic polymerisations carried out isothermally could become explosive.

The Chain-transfer Reactions.—Each of the reactions (V) represented in the scheme above is equivalent to a chain-transfer mechanism, because in each case either the catalytic complex or an actual growing chain is reproduced. Eley and Richards (*loc. cit.*) have recently shown that chain transfer can occur in the ionic polymerisation of vinyl ethers. Horrex and Perkins (*Nature*, 1949, **163**, 486) have shown that chain transfer probably takes place in the low-temperature polymerisation of *iso*butene by boron trifluoride when this is inhibited by olefins, and A. G. Evans and Meadows (*loc. cit.*) have found that in the polymerisation of gaseous *iso*butene by boron trifluoride and acetic acid at room temperature there is a very high degree of chain transfer. The same phenomenon has been found in the course of the present work. Approximately 1×10^{-3} mole of $TiCl_4,CCl_3{\cdot}CO_2H$ complex in contact with gaseous *iso*butene at room temperature produced about 2×10^{-3} mole of polymer of mean molecular weight 400. In the polymerisations carried out at low temperatures the number of moles of polymer produced is usually smaller than the number of moles of co-catalyst. The presence of double bonds in the polymers formed at higher temperatures which was found by Dainton and Sutherland (*J. Polymer Sci.*, 1949, **4**, 37) and which was confirmed by Flett and Plesch (in the press) for poly*iso*butenes of mean molecular weight up to at least 10^6 can be considered as evidence of chain transfer only if the number of moles of polymer is greater than the number of moles of co-catalyst. In view of the possible occurrence of termination (IV*b*), the mere presence of double bonds is not evidence for chain transfer.

The presence of other olefins during the polymerisation of *iso*butene reduces the molecular

weight of the polymer without necessarily affecting the rate (Horrex and Perkins, *loc. cit.*; Thomas *et al.*, *loc. cit.*). Therefore if olefins are produced as products of the normal reaction we could expect a self-poisoning effect by reaction (V*c*). Since according to this scheme the catalytic complex is regenerated there will probably be no effect on the rate but anomalous molecular weights and disappearance of terminal double bonds as the reaction goes to completion might be observable. Double bonds resulting from reaction (V*c*) are probably too inaccessible to take part in any further reaction.

Further work on co-catalysts and inhibitors for this polymerisation is in progress, and the kinetics of isothermal polymerisations are being studied.

I would like to express my gratitude to Professor M. Polanyi, F.R.S., for his help and encouragement in this work, and to my colleagues for many helpful discussions. I thank also Messrs. Imperial Chemical Industries (Billingham) Ltd. for kindly supplying the *iso*butene, the Anglo-Iranian Oil Co. Ltd. for funds which materially assisted the progress of this work, and the Editor of "*Research*" for permission to reproduce Fig. 4.

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105. *The Apparent Dipole Moments of the Chlorinated Methanes in the Liquid, Dissolved, and Gaseous States.*

By G. A. BARCLAY and R. J. W. LE FÈVRE.

For CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4, the apparent moments (Debye–Clausius–Mosotti formulæ) in the states given in the title are respectively: 1·19, 1·69, 1·86; 1·14, 1·55, 1·57; 0·97, 1·13, 1·01; and *ca.* 0, 0, 0 (solvent: C_6H_6 in each case). Methylene dichloride thus slightly contravenes those "rules" which relate μ_{gas} to $\mu_{solution}$ *via* the algebraic sign of the Kerr constant of the solute, which for this substance is negative.

Certain empirical equations for the solvent effect are examined and the generality of their applicability tested.

THE substances indicated by the title form a set of readily available related simple structures which are representative of the three chief types of solute molecules encountered in dipole moment measurements, *i.e.*, those with extension respectively (*a*) along the dipole axis (CH_3Cl), (*b*) unequally around it (CH_2Cl_2), (*c*) symmetrically across it ($CHCl_3$), and (*d*) equally about a centre (CCl_4). The original purpose of the present communication was to examine the variations with state of the apparent moments (as indicated by the Debye–Clausius–Mosotti formulæ) of these four compounds *vis à vis* the algebraic signs and magnitudes of their Kerr constants.

Several of the data required for our discussion were already on record in the literature (references below); we have checked or supplemented these where necessary. Dielectric-constant measurements on the system C_6H_6–CH_2Cl do not appear to have been made previously. Table I shows the relevant polarisations at 25° and the moments calculated therefrom, the temperature-invariant term of the Debye equation being used as the true distortion polarisation ($_DP$) in each case.

Table II contains ratios extracted from Table I, together with Sachsse's values for the molar Kerr constants (*Physikal. Z.*, 1935, **36**, 357). It is apparent at once that "rules" requiring the sign of the solvent effect, $\delta\mu$, to be a reversal of that for the electric double refraction, K, are disobeyed by methylene dichloride as a solute, and by this substance and chloroform as undiluted liquids. The comparisons involving *pure* chloroform deserve comment since hitherto this liquid has been regarded as one for which $\delta\mu$ is positive (or $\mu^2_{liq.}/\mu^2_{gas}$ greater than unity; Le Fèvre and Le Fèvre, *J.*, 1935, 1747; Le Fèvre, "Dipole Moments," Methuen, 1938, p. 45; Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374). Such a result was due to the use of the molecular refraction as an approximation for the true distortion polarisation (thus if, in Table I, instead of $_DP_{CHCl_3} = 25{\cdot}3$ c.c., $[R_L]_D = 21{\cdot}4$ c.c. were used, μ would appear as 1·0$_7$ D., *i.e.*, 0·06 D. larger than μ_{gas}). With methylene dichloride, however, μ_{gas} exceeds $\mu_{liq.}$ by both methods of calculation ($\mu_{liq.} = 1{\cdot}22$ with $[R_L]_D = 16{\cdot}4$; Vogel, *J.*, 1948, 1849). The "negative" solvent action of benzene on this substance, although slight, resembles in order that reported recently for sulphur dioxide (Le Fèvre and Ross, *J.*, 1950, 283). Thus there are now known two substances, showing definitely negative Kerr constants, for which the $\mu_{C_6H_6}/\mu_{gas}$ ratios are *less than unity*.

TABLE I.

P in c.c.; μ in D.	CH_3Cl.	CH_2Cl_2.	$CHCl_3$.	CCl_4.	*P* in c.c.; μ in D.	CH_3Cl.	CH_2Cl_2.	$CHCl_3$.	CCl_4.
$({}_TP)_{gas}$ ...	85·3	70·6	46·3	28·1	$({}_0P)_{liq.}$* ...	29·1	26·8	19·4	*ca.* 0
${}_DP$	13·6	20·0	25·3	28·1	$({}_0P)_{liq.}$† ...	71·7	60·1	31·9	2·3
$({}_0P)_{gas}$ ...	71·7	50·6	21·0	*ca.* 0	ρ_{gas}	$1·8_5$	$1·5_7$	$1·0_1$	*ca.* 0
$({}_TP_\infty)_{C_6H_6}$	72·4	69·4	51·7	28·0	$\rho_{C_6H_6}$	$1·6_6$	$1·5_3$	$1·1_2$	*ca.* 0
$({}_0P_\infty)_{C_6H_6}$	58·6	49·4	26·4	*ca.* 0	$\rho_{liq.}$*	$1·1_9$	$1·1_4$	$0·9_7$	*ca.* 0
$({}_TP)_{liq.}$ ...	42·7	46·6	44·7	28·0	$\rho_{liq.}$†	$1·6_4$	$1·7_4$	$1·2_4$	0·3

* Apparent values by the Clausius–Mosotti–Debye equations.
† Apparent values by the Onsager equation.

TABLE II.

	CH_3Cl.	CH_2Cl_2.	$CHCl_3$.		CH_3Cl.	CH_2Cl_2.	$CHCl_3$.
$\mu^2_{solv.}/\mu^2_{gas}$	0·820	$0·97_6$	1·26	$*\delta_{\rho_{calc.}}/\rho_{gas}$	−0·360	−0·274	−0·040
$*\delta_{\rho_{solv.}}/\rho_{gas}$	$-0·09_{14}$	$-0·01_3$	+0·119	$K \times 10^{12}$	41	−13·7	−28
$\mu^2_{liq.}/\mu^2_{gas}$	0·406	0·530	0·924				

* $\delta\mu$ = $\mu_{solution}$ or $\mu_{liq.\ or\ gas}$ minus μ_{gas}.

EXPERIMENTAL.

Data Sources.—Those relating to total polarisations are listed in three groups, by state. In each case the reference providing information for Table I is placed first, others following in chronological order. Although a complete survey of the literature was made, we here omit obviously incorrect or rough determinations.

(*a*) *Gaseous Dielectrics.*—Some authors quote equations for $(\varepsilon - 1)_{\rho}$ or $({}_TP_{gas})_{\rho}$. Others give individual observations of $(\varepsilon - 1)_{\rho}$. The forms used are indicated.

μ, D.	Results as :	Authors.	Reference.
	Methyl chloride.		
1·86	$P = 13·6 + 21{,}351/T$	Smyth and McAlpine	*J. Chem. Physics*, 1934, **2**, 499.
1·97	$\varepsilon - 1 = 0·0_5116 + 2·825/T$	Sänger	*Physikal. Z.*, 1926, **27**, 556.
1·69	Individual $(\varepsilon - 1)_{\rho}$	Sircar	*Indian J. Physics*, 1928, **3**, 197.
1·89	One $(\varepsilon - 1)_{gas}$ value	(Calc. by Höjendahl, Thesis, Copenhagen, 1928, from data by Pohrt, *Ann. Physik*, 1913, **42**, 569).	
1·86	$P = 14·72 + 21{,}208/T$	Sänger and Steiger	*Helv. Physica Acta*, 1929, **2**, 130, 411.
1·86	Final μ only	Sänger	*Ibid.*, 1930, **3**, 161.
1·86	Individual $(\varepsilon - 1)_{\rho}$	Fuchs	*Z. Physik*, 1930, **63**, 824.
1·86	$P = 14·1 + 21{,}390/T$	Sänger, Steiger and Gächter	*Helv. Physica Acta*, 1932, **5**, 200.
1·92	$P = 8·66 + 22{,}730/T$	Ramaswamy	*Proc. Indian Acad. Sci.*, 1936, *A*, **4**, 108.
	N.B.—Mean of last 8 values = 1·86 D.		
	Methylene dichloride.		
1·58	$P = 19·98 + 15{,}064/T$	Maryott, Hobbs, and Gross	*J. Amer. Chem. Soc.*, 1941, **63**, 659.
1·59	$\varepsilon - 1 = 0·0_5{}1356 + 1·170/T$	Sänger	*Loc. cit.*, 1926.
1·62	Individual $(\varepsilon - 1)_{\rho}$	Mahanti and Sengupta	*J. Indian Chem. Soc.*, 1928, **5**, 673.
1·53	$P = 18·74 + 14{,}470/T$	Ramaswamy	*Loc. cit.*
	N.B.—Mean of last 3 values = 1·58 D.		
	Chloroform.		
1·01	$P = 25·28 + 6251/T$	Maryott, Hobbs and Gross	*Loc. cit.*
0·95	$\varepsilon - 1 = 0·0_5{}2127 + 0·4328/T$	Sänger	*Loc. cit.*, 1926.
1·05	Individual $(\varepsilon - 1)_{\rho}$	Sircar	*Loc. cit.*
0·99	$P = 24·72 + 6096/T$	Ramaswamy	*Loc. cit.*
1·02	$P = 24·92 + 6491/T$	Ramaswamy	*Loc. cit.*
	N.B.—Mean of last 4 values = 1·00 D.		
	Carbon tetrachloride.		
0	$\varepsilon - 1 = 0·0_5{}2645 + 0·0348/T$	Sänger	*Loc. cit.*, 1926.
0	$P = 28·14 + 0/T$	Ramaswamy	*Loc. cit.*

(*b*) *Solutions in Benzene.*—These are tabulated under self-explanatory headings except that col. 5 shows the moments obtained *via* the true distortion polarisations (cf. Table I), while col. 6 contains those from the figures given by the original authors, who used for ${}_EP + {}_AP$ the refractivities in parentheses.

Substance.	Temp.	No. of solns. examined.	$_{\infty}P_2$, c.c.	μ, D.	μ, D.	References.
CH_3Cl	25°	6	72·4	1·69	1·72(11·5) *	Present Work.
CH_2Cl_2	25	12	69·4	1·55	1·60(16·4) *	Present Work.
	25	5	70·0	1·56	1·61(15·8)	Mahanti and Das Gupta (*J. Indian Chem. Soc.*, 1929, **6**, 411).
	25	1	66·3	1·50	1·55(16·2)	Müller and Sack (*Physikal. Z.*, 1930, **31**, 815).
	20	1	68·1	1·51	1·59(15)	Müller (*ibid.*, 1933, **34**, 689).
$CHCl_3$	25	15	51·7	1·13	1·21(21·4)	Le Fèvre (*Trans. Faraday Soc.*, 1950, **46**, 1).
	25	4	47·5	1·04	1·10(21·3)	Williams and Krchma (*J. Amer. Chem. Soc.*, 1927, **49**, 1676).
	18	3	55·4	1·19	1·27(21·3)	Hassel and Uhl (*Z. physikal. Chem.*, 1930, *B*, **8**, 187).
	25	1	51·2	1·12	1·18(21·3)	Müller and Sack (*loc. cit.*).
	20	1	51·9	1·12	1·21(21·2)	Müller (*loc. cit.*).
	25	4	52·1	1·14	1·22(21·4)	Le Fèvre and Russell (*J.*, 1936, 491).
CCl_4	25	6	28·0	0	0 (26·5) *	Present Work.
	25	4	28·3	0	0 (26·3)	Williams and Krchma (*loc. cit.*).
	20	1	28·7	0	0 (26·1)	Müller (*Physikal. Z.*, 1933, **34**, 689).

* Values from Vogel (*J.*, 1948, 1842.)

(*c*) *Pure Liquids.*—

Substance.	ϵ^{25}.	d_4^{25}.	$_{\infty}P_{25}$, c.c.	Reference.
CH_3Cl	9·68	0·878$_5$	42·7	Extrapolated from values recorded by Ulrich and Nespital (*Z. physikal. Chem.*, 1932, *B*, **16**, 221), Morgan and Lowry (*loc. cit.*), and Goss (*J.*, 1934, 696, 1467).
CH_2Cl_2	8·93	1·3169	46·8	Present work.
	8·92	1·3175	46·7$_5$	Morgan and Lowry (*loc. cit.*).
$CHCl_3$	4·724	1·4790	44·7	Le Fèvre and Rayner (*J.*, 1938, 1921; cf. Ball, *J.*, 1930, 570).
	4·642	—	—	Harris (*J.*, 1925, **127**, 1049).
	4·770	1·4796	45·0	Williams and Krchma (*loc. cit.*).
	4·670	1·4780	44·4	Smyth and Morgan (*loc. cit.*).
	4·899	—	—	Matsuike (*Proc. Imp. Acad. Tokyo*, 1929, **5**, 29).
	4·745	1·4800	44·8	Morgan and Lowry (*loc. cit.*).
	4·722	1·4797	44·7	Jenkins (*J.*, 1934, 480).
	4·709	—	—	Davies (*Phil. Mag.*, 1936, **21**, 1).
CCl_4	2·2270	1·5844	28·18	Le Fèvre (*Trans. Faraday Soc.*, 1938, **34**, 1127).
	2·219	—	—	Harris (*loc. cit.*).
	2·230	1·5835	28·24	Williams and Krchma (*loc. cit.*).
	2·210$_5$	1·584$_3$	27·92	Stranathan (*Physical Rev.*, 1928, **31**, 653).
	2·197	—	—	Matsuike (*loc. cit.*).
	2·231	1·5820	28·27	Morgan and Lowry (*loc. cit.*).
	2·225	1·5836	28·17	Fairbrother (*J.*, 1932, 43).
	2·227$_7$	1·5848	28·19	Jenkins (*loc. cit.*).
	2·226$_4$	—	—	Davies (*loc. cit.*).
	2·2276	1·5846	28·18	Miller (*J. Amer. Chem. Soc.*, 1942, **64**, 117).

Present Measurements.—Methyl chloride (from methyl alcohol, zinc chloride, and hydrochloric acid; Morris and Taylor, *J. Amer. Chem. Soc.*, 1924, **46**, 755), dried by passage through 10% potassium hydroxide solution, concentrated sulphuric acid, and a tower of solid potassium hydroxide, was dissolved in sodium-dried benzene, etc., as described by Le Fèvre and Ross (*loc. cit.*) for sulphur dioxide. The methylene dichloride was a commercial specimen. After standing for several hours over calcium chloride, it was distilled (b. p. 40·1°; d_4^{25} 1·3169) before use. Measurements were made by usual procedures (Le Fèvre, "Dipole Moments," Methuen, 2nd Edn., 1948, pp. 31—42) on apparatus already noted (Le Fèvre and Ross, *loc. cit.*; Calderbank and Le Fèvre, *J.*, 1948, 1949). Extrapolation methods, and symbols used, are explained elsewhere (*Trans. Faraday Soc.*, 1950, **46**, 1) and need not be repeated here.

Methyl chloride in benzene at 25°.

10^5w_1.	ϵ^{25}.	$\alpha\epsilon_2$.	d_4^{25}.	βd_2.	10^5w_1.	ϵ^{25}.	$\alpha\epsilon_2$.	d_4^{25}.	βd_2.
0	2·2725	—	0·87378	—	2810	2·4367	5·84	0·87552	0·0619
1370	2·3563	6·12	0·87459	0·0591	2876	2·4384	5·77	0·87560	0·0633
2080	2·3944	5·86	0·87507	0·0620	3418	2·4817	6·12	0·87605	0·0664
2558	2·4246	5·95	0·87540	0·0633					

Whence mean $\alpha\epsilon_2 = 5·94$; mean $\beta d_2 = 0·0626$; and $_{\infty}P_2 = 72·4$ c.c.

Methylene chloride in benzene at 25°.

10^5w_1.	ϵ^{25}.	α_{12}.	d_4^{25}.	βd_{12}.	10^5w_1.	ϵ^{25}.	α_{12}.	d_4^{25}.	βd_{12}.
821·6	—	—	0·87599	0·280	6,794	2·4925	3·14	0·89326	0·286
1204	2·3108	3·18	—	—	6,830	2·5117	3·50	0·89365	0·291
1374	2·3120	2·89	0·87769	0·285	8,933	2·5565	3·18	—	—
1722	2·3289	3·27	0·87875	0·289	9,443	2·6027	3·50	0·90128	0·291
2795	2·3602	3·17	0·88217	0·300	12,660	2·6965	3·35	0·91165	0·299
2859	2·3641	3·20	0·88219	0·294	15,010	2·7781	3·37	0·91964	0·306
5088	2·4357	3·21	0·88867	0·293					

Whence (by least squares) $\alpha_{12} = 3·12 + 2·13w_1$; $\beta d_{12} = 0·286 + 0·107w_1$; and $_{\infty}P_1 = 69·4$ c.c.

The dielectric constant of pure methylene chloride at 25° (*viz.*, 8·93) was read from a graph of condenser reading against $(\epsilon - 1)$, obtained from the following standards: air, $\epsilon = 1$; C_6H_6, $\epsilon = 2·27$; C_6H_5Cl, $\epsilon = 5·61$; o-$C_6H_4Cl_2$, $\epsilon = 9·82$.

*Carbon tetrachloride in benzene at 25°.**

10^5w_1	0	9251	11,034	18,951	20,522	30,908	33,461
ϵ^{25}	2·2725	2·2724	2·2724	2·2723	2·2723	2·2718	2·2714
d_4^{25}	0·87378	0·87759	0·87810	0·88131	0·88189	0·88609	0·88710

$\Sigma(\epsilon_{12} - \epsilon_2)/\Sigma w_1 = -0·019$; $\Sigma(d_{12} - d_2)/\Sigma w_1 = 0·398$; whence $_{\infty}P_1 = 28·0$ c.c.

* Recorded at University College, London, 1938—39, with the apparatus of Le Fèvre and Russell (*Trans. Faraday Soc.*, 1947, **43**, 374).

Discussion.

Attempts to relate the variation of the apparent moment of a substance with its state (compare Glasstone, *Ann. Reports*, 1936, **33**, 117, for references not explicitly given here) may be roughly divided into four classes, *viz.*, (*a*) empirical methods of correction for solvent influence, (*b*) *a priori* introduction of factors, for solute and/or for medium, not included in the Clausius–Mosotti–Debye treatment, (*c*) new fundamental models for dielectric polarisation, and (*d*) the addition to the approaches under (*b*) and (*c*) of the conception of hindered rotation, or quasi-crystallinity, in liquids.

Proposals under (*a*) by Müller, Jenkins, Arkel and Snoek, Sugden, Henriquez, *et al.*, like those under (*d*) by Debye (*Physikal. Z.*, 1935, **36**, 100, 193; *Chem. Rev.*, 1936, **19**, 171), Fowler (*Proc. Roy. Soc.*, 1935, *A*, **149**, 1), Kincaid and Eyring (*J. Chem. Physics*, 1938, **6**, 620), and Kirkwood (*J. Chem. Physics*, 1939, **7**, 911; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 315), cannot—in the forms as published—cover those cases (Le Fèvre and Russell, *loc. cit.*; Le Fèvre and Ross, *J.*, 1950, 283; Le Fèvre, Mulley, and Smythe, *J.*, 1950, 290) where $\mu_{solu.}/\mu_{gas}$ or $\mu_{liq.}/\mu_{gas}$ are greater than unity. Onsager's equation, which falls under (*c*), if used literally, fails with methylene chloride and chloroform (cf. Table 1); Wilson's modification (*Chem. Rev.*, 1939, **25**, 377) of it to cover the anisotropy of the solute molecules is an improvement, but one of limited practical usefulness since for most compounds Kerr constant polarisability data are lacking.

In group (*b*) there are the *a priori* treatments of Weigle, Higasi, and Frank, together with others involving the constants ψ and θ of Raman and Krishnan (*Proc. Roy. Soc.*, 1928, *A*, **117**, 589; cf. Goss, *Trans. Faraday Soc.*, 1934, **30**, 751; Le Fèvre and Le Fèvre, *J.*, 1935, 1747; and the criticisms of Jenkins and Bauer, *J. Amer. Chem. Soc.*, 1936, **58**, 2435). In a general way, these approaches have successfully forecast whether $\mu_{solu.}/\mu_{gas}$ for a given molecule is above or below unity. In cases where the structure can be credibly regarded as spheroidal, the (*b*) theories have often given approximately quantitatively correct ratios. Unfortunately, in many practical instances, however, neither the ellipsoids defining the anisotropy of polarisability or of "shape" are bodies of rotation. The following table illustrates this point

	(1).			(2).			(3).		
	b_1.	b_2.	b_3.	b_1.	b_2.	b_3.	*A*.	*B*.	*C*.
CH_2Cl	1	0·764	0·764	1	0·827	0·827	1	0·750$_5$	0·750$_5$
CH_2Cl_2	—	—	—	1	1·193	0·952	1	1·488	0·878
$CHCl_3$	1	1·349	1·349	1	1·233	1·233	1	1·585	1·585
CCl_4	—	—	—	—	—	—	—	—	—

for the chloromethanes. Under (1) are given the relative polarisabilities recorded for the gaseous materials (Stuart and Volkmann, *Ann. Physik*, 1933, **18**, 140), under (2) the same but for solutions in carbon tetrachloride (Sachsse, *Physikal. Z.*, 1935, **36**, 357), and under (3) the relative effective

dimensions (see later) of the molecules. In each case the property measured along the dipole axis is taken as unity.

Several of the relations previously published for solvent action in this field can be cast into general forms typified by: $\mu^2_s/\mu^2_g = 1 + A(\varepsilon - 1)/(\varepsilon + 2)$. For CH_2Cl, CH_2Cl_2, and $CHCl_3$, the results in Table I require A to be *ca.* $-0{\cdot}60$, $-0{\cdot}067$, and $+0{\cdot}87$, respectively. We find that these figures correspond to exp $x^2 - (n^2_1)_{RH}/(n^2_1)_{RH}$, where n^2_{RH} is calculated from the distortion polarisation of solvent or solute, *i.e.*, $(n^2_{RH} - 1)M/(n^2_{RH} + 2)d_{RH}$, and x^2 is obtained by the following procedure: Scale drawings are constructed from the known *X*-ray or electron-diffraction data (in the cases just named these are from Sutton and Brockway, *J. Amer. Chem. Soc.*, 1935, **57**, 473; in other instances below, dimensions are those recommended by Pauling and Huggins, *Z. Krist.*, 1934, **87**, 205, and Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1941, **63**, 37) and the "Wirkungsradien" of Stuart (*Z. physikal. Chem.*, 1935, *B*, **27**, 350) superimposed. The maximum measurements along, and in the two perpendicular directions to, the axis of the molecular resultant dipole moment are then read off and recorded as ratios with $A = 1$. Length A is consistently taken parallel to $\mu_{resultant}$; of B and C (if different), C is made the lesser, x^2 follows as $(C^2 - A^2)/A^2$ when $A > B$ or C, $(C^2 - A^2)/B^2$ when $A < B > C$ and $(C^2 - A^2)/C^2$, when $A < B$ or C. The equation indicated is therefore:

$$\mu^2_{calc.}/\mu^2_{gas} = 1 + (\varepsilon - 1)[(\exp x^2 - (n^2_1)_{RH}/(n^2_1)_{RH}]/(\varepsilon + 2) \quad . \quad . \quad . \quad (1)$$

This is tested in Table III. It is seen that the calculated and observed ratios are in reasonable agreement.

TABLE III.

Substance.	*B*.	*C*.	n^2_{RH}.	Exp $x^2 - (n^2_1/n^2_1)_{RH}$.	${}_0P_s/{}_0P_g$ (calc.).	${}_0P_s/{}_0P_g$ (found).
CH_2Cl	0·721	0·721	1·929	−0·598	0·82	0·82
CH_2Cl_2	1·488	0·878	2·349	−0·077	0·98	0·98
$CHCl_3$	1·585	1·585	2·368	+0·855	1·26	1·26
$C_6H_5NO_2$	0·752$_5$	0·562$_5$	2·633	−0·369	0·89	0·87 [1]
C_6H_5Cl	0·787	0·391	2·554	−0·481	0·86	0·84 [2]
C_6H_5Me	0·751$_5$	0·485	2·215	−0·573	0·83	0·84 [3]
SO_2	1·453	0·895	1·911	−0·293	0·91	0·99 [4]
Paraldehyde	2·50	2·50	2·499	1·41	1·42	1·69 [5]

References.—*Dipole moment values*: (1) $\mu_g = 4{\cdot}24$ (Groves and Sugden, *J.*, 1934, 1094; 1935, 971), $\mu_{Benzene} = 3{\cdot}95$ (Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). (2) $\mu_g = 1{\cdot}73$ (Groves and Sugden, *loc. cit.*), $\mu_{Benzene} = 1{\cdot}59$ (Le Fèvre, *loc. cit.*). (3) $\mu_g = 0{\cdot}37$ (McAlpine and Smythe, *J. Amer. Chem. Soc.*, 1933, **55**, 453; Baker and Groves, *J.*, 1939, 1144), $\mu_{Benzene} = 0{\cdot}34$ (Le Fèvre, Le Fèvre, and Russell, *J.*, 1935, 480). (4) $\mu_g = 1{\cdot}62$ (Le Fèvre, Ross, and Smythe, *J.*, 1950, 276), $\mu_{Benzene} = 1{\cdot}61$ (Le Fèvre and Ross, *J.*, 1950, 283). (5) $\mu_g = 1{\cdot}44$ (Le Fèvre, Mulley, and Smythe, *J.*, 1950, 290), $\mu_{Benzene} = 1{\cdot}87$ (*idem*, *ibid.*).

Special structures: Chlorinated methanes, Brockway and Sutton, *J. Amer. Chem. Soc.*, 1935, **57**, 473; nitrobenzene, James, King, and Horrocks, *Proc. Roy. Soc.*, 1935, *A*, **153**, 225; paraldehyde, see Le Fèvre, Mulley, and Smythe, *loc. cit.*, for refs.; sulphur dioxide, Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1940, **62**, 1270.

We next explored the possibility of modifying the equation of Le Fèvre and Le Fèvre (*J.*, 1935, 1747) along lines obvious from the discussion of the Raman–Krishnan expression by Govinda-Rao (*Proc. Indian Acad. Sci.*, 1935, **1**, 498), *viz.*, by taking 0 as approximately equal to $\mu^2_1 S_1$ and writing S_1 as $4\pi(\delta - 1/3)$, so that

$${}_0P_s/{}_0P_g = 1 + 3\theta(\varepsilon - 1)/(\varepsilon + 2)4\pi\mu^2 = 1 + 3(\delta - 1/3)(\varepsilon - 1)/(\varepsilon + 2) \quad . \quad (2)$$

Estimations of δ were made by using the x^2 values as before and applying them in the equations of Maxwell ("Electricity and Magnetism," Vol. 2, Oxford, 1892, Article 438; cf. also Lord Rayleigh, "Scientific Papers," **4**, 307; Mascart and Joubert, "Leçons," 1896, paras. 52, 53, 276) as follows: (when x^2 positive) $\delta = (1/x^2) - \{(1 - x^2)^{\frac{1}{2}}$ arc sin $x\}/x^3$, or (when x^2 negative, regarding x^2 as $(-1)y^2$] $\delta = [(1 - y^2)/y^3][(1/2\,y)\ln\{(1 + y)/(1 - y)\} - 1]$. Table IV contains the results for a representative range of molecules; $3\delta - 1$, just as exp $x^2 - (n^2_1)_{RH}/(n^2_1)_{RH}$ (Table III), correctly forecasts the type of solvent effect; the former quantity, however, does not run parallel to it. Since intuitively it seemed that the appropriate relation might be ${}_0P_s/{}_0P_g$ (or μ^2_s/μ^2_g) $= 1 + f(\varepsilon, n^2_{RH})(3\delta - 1)$ many different types of $f(\varepsilon, n^2_{RH})$ were tried. Of these, several were promising, *e.g.*,

$${}_0P_s/{}_0P_g = 1 + {}_DP_1(\varepsilon_2 + 2)(3\delta - 1)d_1/M_1(\varepsilon_2 - 1) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where ${}_DP_1$ is the distortion polarisation of the solute and M_1 its molecular weight. Six examples will show, however, that (3) acts in the right sense, but excessively :

	3δ − 1.	${}_oP_2/{}_oP_2$ (calc.).	${}_oP_2/{}_oP_2$ (found).		3δ − 1.	${}_oP_2/{}_oP_2$ (calc.).	${}_oP_2/{}_oP_2$ (found).
CH_3Cl	−0·274	0·78	0·82	Paraldehyde...	+0·764	1·75	1·69
CH_2Cl_2	−0·055	0·96	0·98	SO_2	−0·238	0·88	0·99
$CHCl_3$	+0·428	1·27	1·26	$C_6H_5{\cdot}NO_2$ ...	−0·409	0·65	0·87

If our " δ " is used in place of the " ξ " of the Ross–Sack equation,

$$\frac{\mu_2}{\mu_g} = \frac{3\varepsilon}{(\varepsilon+2)} \frac{1+(n^2_{RH}-1)\delta}{\varepsilon+(n^2_{RH}-\varepsilon)\delta} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

cited in a previous paper (*J.*, 1950, 283), the ratios indicated are :

	${}_oP_2/{}_oP_2$ (calc.).		${}_oP_2/{}_oP_2$ (calc.).
CH_3Cl	0·80	Paraldehyde	1·56
CH_2Cl_2	0·98	SO_2	0·81
$CHCl_3$	1·29	$C_6H_5{\cdot}NO_2$	0·81

Expressions Useful in Practice.—To the above attempts may be urged the objections : (*a*) that the ${}_DP$ for a given substance is difficult to measure accurately (examples of this occur in the tables on p. 557; sometimes the A of the Debye equation can be obviously too small without the μ_{gas} value becoming grossly incorrect, *e.g.*, Ramaswamy, *Proc. Indian Acad. Sci.*, 1936, *A*, **4**, 108, gives for acetone $P = 6 + 53650/T$, whence $\mu = 2{\cdot}95$; yet $[R_L]_D$ for this substance is *ca.* 16 c.c.); and (*b*) that knowledge of n^2_{RH} implies the existence of experiments from which μ_{gas} should be calculable directly. Since our underlying motive, for reasons set out elsewhere (" Dipole Moments," Methuen, 1938, p. 52), is to search for an *a priori* method whereby μ_{gas} may be estimated from observations on solutions, we regard (*b*) as serious, and proceed therefore to show the measure of success to be achieved with the accessible quantity n_D^2, instead of n^2_{RH}, in equations (1)—(4).

Table IV summarises our computations for benzene ($n_D^2 = 2{\cdot}2417$ at 25°) as solvent. It

TABLE IV.

	B.	*C.*	ε_2.	δ.	μ_{CCl_4}.	n_D^2.	μ_{gas} calc., *via* (1).	(2).	(3).†	(4).	μ_{gas}, obs.
CH_3Cl ...	•	•	−0·520	0·242	1·69	1·7510 (*a*)	1·89	1·76	1·86	1·92	1·86
CH_2Cl_2 ...	•	•	−0·103	0·315	1·55	2·0295	1·59	1·56	1·57	1·61	1·57
$CHCl_3$ ...	•	•	+0·602	0·476	1·13	2·0825	1·02	1·06	1·02	1·02	1·01
$CH_3{\cdot}CN$ ...	0·639	0·639	−0·592	0·223	3·11— 3·51	1·800	3·49— 3·94	3·28— 3·70	3·62— 4·08	3·58— 4·04	3·94— 3·98
$CH_3{\cdot}NO_2$	0·865	0·731	−0·466	0·254	3·02— 3·13	1·9040	3·30— 3·42	3·13— 3·56	3·26— 3·38	3·35— 3·47	3·42
$CO(CH_3)_2$	1·270	0·738	−0·282	0·291	2·74	1·8400	2·95	2·79	2·89	2·96	2·83— 3·02
Paralde-hyde ...	•	•	+0·840	0·588	1·87	1·989	1·60	1·68	1·50	1·56	1·44
SO_2	•	•	−0·094	0·254	1·61	1·763 (*b*)	1·70	1·67	1·70	1·81	1·62
$N(CH_3)_3$ ...	1·74	1·74	+0·670	0·489	0·86	1·908	0·78	0·80	0·71	0·79	0·64
$C_6H_5{\cdot}CH_3$	•	•	−0·765	0·168	0·34	2·2320	0·37	0·37	0·48	0·40	0·37
C_6H_5Cl ...	•	•	−0·847	0·132	1·59	2·3180	1·74	1·76	2·23	1·93	1·73
$C_6H_5{\cdot}NO_2$	•	•	−0·684	0·197	3·95	2·4045	4·23	4·22	4·79	4·46	4·24
$C_6H_5{\cdot}CN$	0·693	0·353	−0·875	0·117	3·74— 3·97	2·329	4·09— 4·34	4·16— 4·42	5·77— 6·13	4·62— 4·91	4·39

• See Table III. † Using $[R_L]_D$ instead of ${}_DP$. (*a*) Calc. from $[R_L]_D$ *ex* Vogel's (*loc. cit.*) atomic constants. (*b*) *Ex* $[R_L]_D = 9{\cdot}49$ (Nasini, *Gazzetta*, 1883, **18**, 296) and extrapolated density (Le Fèvre and Ross, *loc. cit.*).

Dipole-moment references additional to those beneath Table III : $CH_3{\cdot}CN$: $\mu_{C_6H_6}$, = 3·11 (Werner, *Z. physikal. Chem.*, 1929, *B*, **4**, 371), 3·51 (Eide and Hassel, *Chem. Ztg.*, 1930, **11**, 2234), 3·16 (Hunter and Partington, *J.*, 1932, 2812), 3·45 (Snoek, *Physikal. Z.*, 1934, **35**, 196), 3·51 (Lewis and Smyth, *J. Chem. Physics*, 1939, **7**, 1085); μ_{gas} = 3·98 (Ramaswamy, *loc. cit.*), 3·94 (Höjendahl, Thesis, 1928), 3·94 (Groves and Sugden, *J.*, 1937, 158). $CH_3{\cdot}NO_2$: $\mu_{C_6H_6}$, (see Faraday Soc. List), μ_{gas} = 3·42 (Smyth and McAlpine, *J. Amer. Chem. Soc.*, 1934, **56**, 1697). Acetone : $\mu_{C_6H_6}$ = 2·74 (see Faraday Soc. List); μ_{gas} = 2·93 to 3·02 (Stuart, *Z. Physik*, 1928, **51**, 490), 2·85 (Zahn, *Physikal. Z.*, 1932, **33**, 686). Trimethylamine : $\mu_{C_6H_6}$ = 0·86, μ_{gas} = 0·64 (Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374; cf. Brockway and Jenkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2036). Benzonitrile : ($\mu_{C_6H_6}$, see Faraday Soc. List), μ_{gas} = 4·39 (Groves and Sugden, *loc. cit.*).

will be noted that, by overall consideration, (1) and (2) seem preferable to (3) and (4) for the four aromatic molecules listed. In most cases (1) and (4) could give better results if n_y were used instead of n_D, since n_y is nearer to n_{∞} than is n_D.

Variation of $\mu_{\text{nitrobenzene}}$ with Solvent.—An empirical "rule," if of correct form, should also forecast the relative effects of different solvents upon a given solute. Table V shows the application of equations (1), (2), and (4), using n_D^2 instead of $n^2_{RR'}$, to the figures conveniently tabulated for nitrobenzene in 12 solvents by Cleverdon and Smith (*Trans. Faraday Soc.*, 1949, **45**, 109) ($\mu_{gas} = 4{\cdot}24$).

TABLE V.

Solvent.	$\epsilon_{25°}$.	$(n_D^2)_{25°}$.	${}_0P_2/{}_0P_2$, calc., *via* eqn.: 1.	2.	4.	${}_0P_2/{}_0P_2$, found.
n-Hexane	1·887	1·8847	0·94	0·91	0·87	0·91
Diisoamyl	1·976	1·9773	0·92	0·90	0·85	0·88
*cyclo*Hexane	2·016	2·0221	0·91	0·90	0·84	0·88
Decalin	2·162	2·16	0·89	0·89	0·81	0·86
Dioxan	2·204	2·0171	0·91	0·89	0·80	0·85
CCl_4	2·228	2·1656	0·89	0·88	0·80	0·86
p-Xylene	2·260	2·2317	0·87	0·88	0·79	0·85
C_6H_6	2·273	2·2417	0·87	0·88	0·79	0·87
CS_2	2·633	2·6360	0·79	0·86	0·71	0·75
Et_2O	4·250	1·8295	0·87	0·79	0·45	0·57
$CHCl_3$	4·722	2·0825	0·80	0·77	0·40	0·55
C_6H_5Cl	5·612	2·3180	0·72	0·75	0·32	0·34

For the nine non-polar solvents, all three relations predict drifts in the direction observed, and for this class (1) seems on the whole superior to (4). The latter, however, alone reflects the effects of the three polar media. Further, it should be repeated again that $n^2_{RR'}$ properly enters (4), *not* n_D^2, which has been utilised only because for most substances it is a recorded (or easily determinable) datum.

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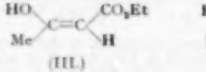
106. *The Polarities of Enols.*

By C. L. ANGYAL and R. J. W. LE FÈVRE.

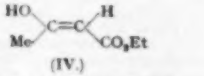
The following dipole moments are recorded (refractivity method; solvent, benzene): anthrone, 3·5 D., ethyl salicylate, 2·7 D., ethyl *p*-hydroxybenzoate, 2·8 D. The moment of anthranol has been estimated as 1·9—2·0 D., *i.e.*, greater than is usual for phenols and naphthols.

THE experiments now recorded were part of an attempt to examine the polarities of enols. The literature reveals that compounds possessing the ·C(OH):CH·CO· unit in a manner such that internal chelation is unlikely for stereo-structural reasons (*e.g.*, dimedone; Hukins and Le Fèvre, *J.*, 1949, 898) are unusually acidic (Taylor and Ewbank, *J.*, 1926, 2818; Bennett, *Chem. and Ind.*, 1926, 960). Phenols, naphthols, etc., also have this quality and can of course be regarded as enols containing the simpler fragment ·C(OH):CH·, yet in no such case has the dipole moment of the corresponding keto-isomeride been recorded. Anthrone (I) and anthranol (II) initially

(I.) (II.)



(III.)



(IV.)

seemed to be a pair of molecules with the desired relationship, since, in solution, they form ultimately an equilibrium with (I) predominating (Beilstein, "Handbuch, etc.," VII, 473; VII*, 257; Meyer, *Annalen*, 1911, 379, 37; 1913, 396, 133; 1920, 420, 113). It later transpired that 100% pure anthranol has never been isolated (Bäckstrom and Beatty, *J. Physical Chem.*, 1931, 35, 2531). We therefore proceeded first to study anthrone itself in benzene, to obtain its specific polarisations at given concentrations (cf. Table I), and then to prepare a succession of separate

quantities of "anthranol," each being analysed by the iodine procedure of Bäckstrom and Beatty (*loc. cit.*) and, simultaneously, submitted to dielectric-polarisation measurements as though it were a single substance. Anthranol contents ranging from 18 to 45% were obtained. On the assumption that only (I) and (II) are concerned, and that a simple mixture rule applies to the observed specific polarisations, moments up to 2 D. were indicated for (II). Reproducibility was, however, poor and continued to be so despite all efforts at improvement.

An estimate of similar order follows from the moment now found for anthranol methyl ether (1·5 D.). Noting that between a phenol and its methyl ether there is commonly a polarity difference of 0·4—0·5 D., it would seem that anthranol has a moment of 1·9—2·0 D., *i.e.*, some 1·5 D. lower than that of anthrone, but notably higher than those of phenol (1·6—1·7) or the two naphthols (1·0—1·5). Attempts to prepare equilibrium mixtures from the ketonic isomeride in benzene or hexane have also been made, but unsuccessfully—a not unexpected result since Meyer's experiments (*Annalen*, 1913, **396**, 133) suggest that strong electrolytes are required. Further, it is relevant that infra-red spectroscopic methods have not shown the presence of any enol form of anthrone in carbon tetrachloride solutions (Flett, *J.*, 1948, 1441).

We have also prepared 9-phenanthrol, but found it to be too sparingly soluble in benzene for measurement.

Dipole Moments of Ethyl Salicylate and p-*Hydroxybenzoate.*—Results for these two compounds are given below. Le Fèvre and Welsh (*J.*, 1949, 1909) estimated the moment of the enolic form of ethyl acetoacetate as 1·7 D. Since this enol might exist as a *cis*- or a *trans*-form, (III) or (IV), it seemed of interest to examine ethyl salicylate and ethyl *p*-hydroxybenzoate—molecules in which the hydroxyl groups and carbethoxy-groups are in the same relative configurations as in (III) and (IV). However, the moments observed (2·7 and 2·8 D., respectively) are too nearly equal to be relevantly useful. It is notable that the parent *o*- and *p*-acids also have similar moments (2·63 and 2·73 D.; Wilson and Wenzke, *J. Amer. Chem. Soc.*, 1935, **57**, 1265).

Experimental.

Materials.—Anthrone was prepared from anthraquinone (*Org. Synth.*, Coll. Vol. I, p. 60) and recrystallised from a benzene–light petroleum (3 : 1); m. p. 152°. Anthranol-containing specimens were obtained and analysed as described by Bäckstrom and Beatty (*loc. cit.*).

Anthranol methyl ether was isolated directly from anthrone by the method of Meyer and Schlösser (*Annalen*, 1920, **420**, 126) and crystallised from a little light petroleum; m. p. 93·5—94·5°.

The ethyl salicylate was a fractionated commercial specimen, b. p. 230—232°. Its *p*-isomer was from a similar source, and was recrystallised from water to m. p. 116°.

Measurements.—These were made by routine methods (cf. *J.*, 1948, 1949) and are tabulated below under the usual headings. The solvent used was benzene throughout.

Anthrone.

10^4w_1	238	373	604	878	972	1177	1489	1657
ε^{25}	2·289	2·299	2·317	2·338$_5$	2·346	2·366	2·389	2·401
d_4^{25}	0·87434	0·87474	0·87528	0·87556	0·87620	0·87676	0·87710	0·87699
P_1 (c.c.)	298	302	312	321	317	329	326	326

Whence $\alpha_2 = 7·02 + 56w_1$; $\beta d_2 = 0·259_5 - 2·9w_1$.

Anthranol methyl ether.

10^4w_1	1277	1836	2451	2928	3660	4064
ε^{25}	2·2907	2·2960	2·3074	2·3111	2·3226	2·3283
d_4^{25}	0·87650	0·87805	0·87940	0·88056	0·88336	0·88419

Whence $\alpha_2 = 1·36_5$ (mean); $\beta d_2 = 0·238$ (mean).

Ethyl salicylate.

10^4w_1	9215	12,060	17,932
ε^{25}	2·3164	2·3501	2·3605
d_4^{25}	0·87620	0·87536	0·87676

Whence $\alpha_2 = 4·82$ (mean); $\beta d_2 = 0·187$ (mean).

Ethyl p-*hydroxybenzoate.*

10^4w_1	2908	3977	4483	5589	5656	6414
ε^{25}	2·2872	2·2942	2·2975	2·3020	2·3028	2·3053
d_4^{25}	0·87468	—	0·87486	—	0·87520	—

Whence $\alpha_2 = 5·31$ (mean); $\beta d_2 = 0·267$ (mean).

Results.—These have been calculated *via* the equations $_{\infty}P_{Y} = M_1[\beta_0(1 - \beta) + C\alpha\varepsilon_2]$, and $\mu = 0{\cdot}221(_{\infty}P_{Y} - R_{\mathrm{D}})^{\frac{1}{2}}$ (at 25°; cf. Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). For benzene, $\beta_0 = 0{\cdot}3409$ c.c. and $C = 0{\cdot}1881$.

Substance.	M_1.	$(\alpha\varepsilon_2)_{\infty\text{ in }0}$.	$(\beta)_{\infty\text{ in }0}$.	$_{\infty}P_{Y}$.	$[R_{\mathrm{D}}]_{\mathrm{D}}$.	μ, D.
Anthrone	194·1	7·02	0·297	302·8	57·5 *	3·46
Anthranol methyl ether	208·1	1·36$_5$	0·272	105·1	61·5 *	1·46
Ethyl salicylate	166·1	4·82	0·214	195·1	44·8 †	2·71
Ethyl *p*-hydroxybenzoate ...	166·1	5·31	0·306	205·2	43·3 *	2·81
					44·1 ‡	2·80

* Calc. from atomic and bond refractions. † Cf. I.C.T., vol. I, 227.
‡ Calc. from ethyl benzoate (42·6 c.c.) and hydroxylic oxygen (1·5 c.c.).

Previous Determinations.—These are as follows: Anthrone: $(_{\infty}P_{Y})_{\mathrm{B}'} = 341$ c.c. in benzene, and $\mu = 3{\cdot}66$ D. using $[R_{\mathrm{D}}]_{\mathrm{D}} = 58$ c.c. (Coomber and Partington, *J.*, 1938, 1444). Ethyl salicylate: $\mu = 2{\cdot}88$ D. in benzene at 40·2° (Hrynakowsky and Kalinowsky, *Compt. rend.*, 1933, **197**, 483; actual polarisations not recorded).

Our results for anthrone differ from those of Coomber and Partington in that their P_1 values, calculated by the usual mixture relation, *increased* with dilution, while ours *decrease*. Consequently, our final μ (3·46) is lower than theirs (3·66). We therefore mention that the above eight anthrone solutions have been examined singly or in pairs on occasions widely spaced over nine months, and have involved different batches of benzene. The contrast cannot easily be ascribed to instrumental "drifts," evaporation, etc.

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107. *The Significance of the Bromine Cation in Aromatic Substitution. Part I. Kinetic Evidence.*

By D. H. DERBYSHIRE and WILLIAM A. WATERS.

Hypobromous acid in mineral acid solutions becomes a powerful brominating agent on account of the production of bromine cations: $H^+ + HOBr \rightleftharpoons (H_2OBr)^+$.

This has been established by brominating sodium toluene-ω-sulphonate with hypobromous acid in the presence of perchloric acid as catalyst and demonstrating that $k_{\psi}/[H^+]$ is very nearly constant. This reaction exhibits a slight negative "primary salt effect," as would be anticipated on the Brønsted–Bjerrum theory of reaction rates.

Bromination of benzoic acid is a similar reaction, but at high concentrations of the acid catalysts (sulphuric and perchloric acid) the bimolecular reaction velocity rises abnormally. This concentration effect can, in the main, be related to the magnitude of Hammett's "acidity function," H_0, but in addition a positive linear "salt effect" can be discerned.

At pH 7—8 the relative brominating powers of molecular hypobromous acid and molecular bromine have been compared, by use of sodium *p*-anisate as the reactant. Molecular bromine appears to be about 2000 times as active an agent as hypobromous acid, but buffer salts evidently react with the latter to produce other complex brominating agents, such as $(Br{\cdot}HPO_4)^-$. The ion $(Br_3)^-$ does not seem to have any detectable brominating power.

MOST investigators of bromine substitution seem to concur with the view (Ingold, Smith, and Vass, *J.*, 1927, 1245; Ingold, *Chem. Reviews*, 1934, **15**, 271) that the polar reactivity of a reagent Br—X depends upon its polarisability to the activated state, $Br^{\delta+}\text{—}X^{\delta-}$, and can be related to the electron affinity of X, thus:

most reactive Br—Cl > Br—Br > Br—OH *least reactive*

Experimental evidence for this view was put forward by Francis (*J. Amer. Chem. Soc.*, 1925, **47**, 2341) who found that at about pH 3 bromine water reacted with *m*-nitrophenol at about a thousand times the speed of free hypobromous acid, and developed the view that the true brominating agent might in each case be the bromine cation, Br^+. Later, however, his conclusions were criticised severely by Alexander (*J.*, 1938, 729) who studied the bromination of phenols on the surface of M/100-sulphuric acid and decided that hypobromous acid was a powerful brominating agent. Much earlier, Stark (*Ber.*, 1910, **43**, 671) reported that hypobromous acid, prepared by shaking a 10% suspension of bromine in water with mercuric oxide and filtering the resulting solution, readily brominated both benzene and toluene, and even converted benzoic into *m*-bromobenzoic acid in 80% yield in 24 hours, whereas bromine water had not this reactivity.

Whilst a number of workers (*e.g.*, Baines, *J.*, **1922**, **121**, 2810; Bartlett and Tarbell, *J. Amer. Chem. Soc.*, **1936**, **58**, 467) have studied the effects of acids and of bromide anions on the equilibrium $Br_2 + H_2O \rightleftharpoons HOBr + H^+ + Br^-$ and their implications for addition and substitution reactions in which polarised molecules, such as $\overset{\delta+}{Br}—\overset{\delta-}{Br}$ rather than free bromine cations, Br^+, may be involved, very few appear to have examined the effects of acids on bromide-free solutions of hypobromous acid. As already reported in brief (*Nature*, **1949**, **164**, 446) we were surprised to find that, though free hypobromous acid has no tendency to react with benzene in dilute aqueous solution, yet on the addition of a mineral acid bromination readily occurs. Evidently the discrepancy between the results of Francis and of Alexander is due to the different acidities of their media; the results of Stark, which we have ourselves confirmed, are also explicable by the fact that his reagent is noticeably acidic; it had pH 2—3 when examined with a pH meter using a glass electrode.

As we have stated (*loc. cit.*), this enhanced reactivity of hypobromous acid in acidic media can be explained by the hypothesis that a rapid reversible reaction with hydrogen ions occurs to give either free bromine cations

$$H^+ + HOBr \rightleftharpoons H_2O + Br^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

or the complex hydrated bromine cation $(H_2OBr)^+$ which is the conjugate acid of the very weak base HOBr:

$$H^+ + HOBr \rightleftharpoons (H_2OBr)^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1b)$$

According to this view, hypobromous acid can behave as a brominating agent in the same way as nitric acid behaves as a nitrating agent (Gillespie and Millen, *Quart. Reviews*, **1948**, **2**, 277), though since the intensely reactive bromine cation can be formed at much lower acidities than can the NO_2^+ cation it may perhaps react as the solvated entity $(H_2OBr)^+$, comparable with the nitracidium ion $(H_2NO_3)^+$ (cf. Halberstadt, Hughes, and Ingold, *Nature*, **1946**, **158**, 514).

Though at first we thought that our experimental findings were novel, we have now seen that exactly the same theory had already been advanced by Shilov and Kaniaev in **1939** [*Compt. rend.* (*Doklady*) *Acad. Sci. U.R.S.S.*, **1939**, **24**, 890] who studied the bromination of the sodium salt of anisole-*m*-sulphonic acid by bromine-free hypobromous acid and showed that it was a second-order reaction which proceeded at a rate which was nearly proportional to the hydrogen-ion concentration of the medium. We now report the results of similar studies of two other aromatic substrates, (*a*) sodium toluene-ω-sulphonate and (*b*) benzoic acid, which we selected because they are not attacked by bromine-water.

In M/200-aqueous solution at 21·5°, sodium toluene-ω-sulphonate does not react with vacuum-distilled, bromide-free hypobromous acid; a mixture at pH 5·18 (glass electrode) showed no drop in titre during 30 minutes. Similar mixtures brought to pH 2 by the addition of perchloric acid had half-reaction periods of about 15 minutes, and the usual tests of varying [HOBr] and [$Ph{\cdot}CH_2{\cdot}SO_3Na$] independently showed that the substitution was a process of first order with respect to each of these reactants and strictly second order as a whole, until the substitution was more than 90% complete.

TABLE I.

Bromination of sodium toluene-ω-sulphonate with hypobromous acid at 21·5° in the presence of perchloric acid.

HOBr, M., $\times 10^{-4}$.	$Ph{\cdot}CH_2{\cdot}SO_3Na$, M., $\times 10^{-2}$.	$HClO_4$, M., $\times 10^{-2}$.	k (bimolec.), observed (mole/l./sec.).	$k_{corr.}$ ($= k_M/HClO_4$).	Total ionic strength, M.
4·73	7·09	9·41	1·28 ± 0·03	13·5$_6$	0·1013
3·47	14·18	4·71	0·66 ± 0·03	14·0$_1$	0·0613
4·38	7·09	4·71	0·675 ± 0·02	14·3$_4$	0·0542
3·91	7·09	2·36	0·345 ± 0·01	14·7$_4$	0·0306
4·08	7·09	0·942	0·146 ± 0·002	15·4$_9$	0·0165
3·99	7·09	0·471	0·0723 ± 0·0006	15·3$_5$	0·0118
4·61	7·09	2·36 × 10^{-4} $HClO_4$ plus 7·06 × 10^{-4} $NaClO_4$	0·313 ± 0·005	13·2$_8$	0·1013
3·39	7·09	2·36 × 10^{-4} $HClO_4$ plus 2·36 × 10^{-4} LiCl	falls with time from 0·23 to 0·17		

From Table I, which summarises our results, it will be seen that $k_{cat.}$ falls by only 12% for a 20-fold change in the perchloric acid concentration, and that it drops steadily as the total ionic strength of the solution is increased. At the dilutions which we have used, both perchloric acid and sodium toluene-ω-sulphonate will be ionised completely. Hence it is the toluene-ω-sulphonate anion which is really substituted and consequently the slight variation of $k_{cat.}$ with dilution is ascribable to a "primary salt effect" (cf. R. P. Bell, "Acid-Base Catalysis," Chap. 2, Oxford, 1941) as the following analysis will show.

Using the Brønsted–Bjerrum theory of reaction rates in solution we may write the equilibrium (1, *b*) above as

$$K = \frac{[H_2OBr^+]}{[H^+].[HOBr]} \times \left\{\frac{f_{H_2OBr}}{f_{H^+} \cdot f_{HOBr}}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

and the substitution reaction as

$$(H_2OBr)^+ + (Ph{\cdot}CH_2{\cdot}SO_3)^- \xrightarrow{k_3} H_2O + H^+ + (C_6H_4Br{\cdot}CH_2{\cdot}SO_3)^- \quad . \quad . \quad (2)$$

Velocity of reaction, $$v = k_3[H_2OBr^+][Ar^-] \times \left\{\frac{f_{H_2OBr^+} \cdot f_{Ar^-}}{f_{tr.}}\right\}$$

where Ar^- is the aromatic anion which is brominated and $f_{tr.}$ is the activity coefficient of the transition complex of the bromination reaction.

Hence $$v = Kk_3[H^+][HOBr][Ar^-] \times \left\{\frac{f_{Ar^-} \cdot f_{H^+} \cdot f_{HOBr}}{f_{tr.}}\right\} \quad . \quad . \quad . \quad . \quad . \quad (B)$$

Writing $k_{bimolec.}$ (measured) $\times$ [HOBr] . [Ar^-] = $k_{cat.}$[H^+][HOBr][Ar^-]

we have $$k_{cat.} = Kk_3\left\{\frac{f_{Ar^-} \cdot f_{H^+} \cdot f_{HOBr}}{f_{tr.}}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (C)$$

At ionic strengths, μ, of under 0·1 mol./litre, the Debye–Hückel expression, $-\log_{10} f_i = Az_i^2\mu^{\frac{1}{2}}$, may be applied for each ion involved, z_i being the charge on each reactant concerned, and hence equation (C) above gives

$$\log_{10} k_{cat.} = \log k_0 - A\mu^{\frac{1}{2}}(z^2_{Ar^-} + z^2_{H^+} - z^2_{tr.}) = \log k_0 - \mu^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad (D)$$

where $\log k_0 = \log_{10} Kk_3$ at infinite dilutions, and μ is the total ionic strength of the solution, since our reaction is one between univalent ions of opposite electrical charge and the theoretical values for A and $z_{tr.}$ are 0·5 and zero respectively. Thus in theory we should expect that the reaction would exhibit a *negative* primary-salt effect, and that the graph of $\log_{10} k_{cat.}$ against $\mu^{\frac{1}{2}}$ should have a limiting gradient of -1 in extremely dilute solution.

Fig. 1 shows that our experimental data accord with an equation of the form (D) though the slope of our plot (found, 0·3) is somewhat lower than the theoretical value. In particular we would draw attention to the fact that point *X* on the graph, corresponding to the experiment in which 0·0706N-sodium perchlorate was added to a 0·0236N-perchloric acid solution so as to bring μ up to the value for the strongest acid catalyst used, falls satisfactorily on the linear plot.

The low gradient of our graph is a natural consequence of the use of solutions somewhat more concentrated than those to which the Debye–Hückel theory is properly applicable, and the deviation may possibly be related to the fact that the transition complex of the attack of the bromine cation on the aromatic nucleus of the toluene-ω-sulphonate anion is not a simple electrically neutral entity but a large dipole, since the bromine cation approaches an uncharged carbon centre remote from the sulphonate group.

It may be noted that a similar negative salt effect seems to influence the substitution studied by Shilov and Kaniaev, in which again the reactants are ions of opposite charge, *viz.*, $(MeO{\cdot}C_6H_4{\cdot}SO_3)^-$ and $(H_2OBr)^+$.

Whilst the addition of sodium perchlorate to a reaction mixture had only a small effect on the reaction velocity, the addition of a smaller concentration of lithium chloride has a much greater effect. It noticeably decreased the rate of bromination and complicated the reaction kinetics. This may be ascribed to the setting up of the further equilibrium (3). It would appear that bromine chloride is a less active brominating agent than the bromine cation

$$(H_2OBr)^+ + Cl^- \rightleftharpoons Br{-}Cl + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(cf. Shilov and Kaniaev, *loc. cit.*). Since similar equilibria (4), giving other electrically neutral brominating agents of uncertain reactivities, would be set up by adding salts of weak acids to

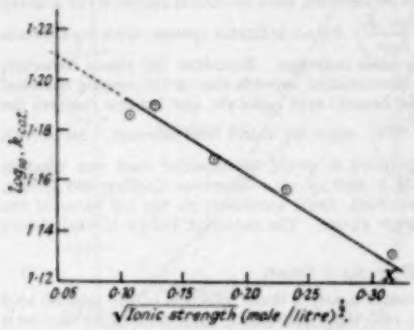
$$(CH_3{\cdot}CO_2)^- + (H_2OBr)^+ \rightleftharpoons CH_3{\cdot}CO_2{-}Br + H_2O \quad . \quad . \quad . \quad . \quad . \quad (4)$$

our reaction mixtures (cf. Mauger and Soper, *J.*, 1946, 71) it is not possible to extend the range of these studies of the reactivity of the bromine cation by carrying out reaction velocity measurements in buffered solutions in the range pH 3—6.

Somewhat different results have been obtained from our study of the bromination of benzoic acid. For this, in order to obtain an adequate concentration of the reactant, we had to use 40% acetic acid as the solvent, and as catalysts we took both perchloric and sulphuric acids over the concentration range 0·1—2·5N. Consequently the aromatic substrate was always the undissociated benzoic acid molecule. Tests showed that even in our most concentrated mineral acid catalysts the acetic acid was not attacked by the bromine cation, and a larger-scale preparation confirmed that *m*-bromobenzoic acid was the main reaction product.

FIG. 1.

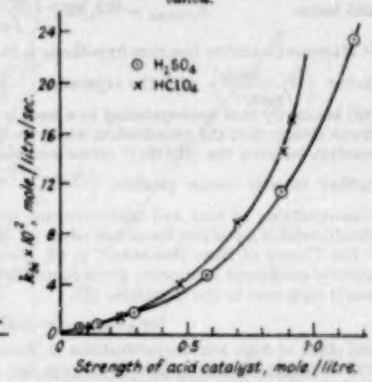
Bromination of sodium toluene-α-sulphonate with hypobromous acid.



Relationship between $\log k_{calc.}$ *and* $\sqrt{\text{ionic strength}}$.

FIG. 2.

Bromination of benzoic acid with bromine cation.



Relationship between $k_{obs.}$ *and acid concentration.*

Fig. 2 shows that both perchloric and sulphuric acid catalyse the reaction between hypobromous and benzoic acids to an extent which is roughly proportional to the mineral acid concentration up to 0·3N., but that at high acid concentrations the value of $k_{calc.}$ increases as [Acid] increases, and sulphuric acid then becomes somewhat less effective as a catalyst than perchloric acid.

Though the Debye–Hückel theory is unable to predict the nature of the salt effects which influence reactions between ions and neutral molecules, an enhanced catalytic effect at high acid concentrations can be expected from analogy with hydrogen-ion-catalysed reactions, such as sucrose hydrolysis, in strong mineral acid solutions. For such reactions Hammett (*Chem. Reviews*, 1935, **16**, 67; "Physical Organic Chemistry," Chap. 9, New York, 1940; Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 830) from studies of indicators of the type $I + H^+ \rightleftharpoons HI^+$ has defined expressions (E) for experimentally measurable "acidity

$$H_0 = pK_a - \log_{10}\frac{[HI^+]}{[I]} = -\log_{10}\left\{a_{H^+}\frac{f_I}{f_{HI^+}}\right\}; \text{ and } h_0 = a_{H^+}\frac{f_I}{f_{HI^+}} \quad . \quad . \quad . \quad (E)$$

functions" H_0, h_0, which were found to be independent of the nature of the indicator chosen. He therefore suggested that in strong acid solutions h_0 might be used to replace the activity coefficient factors in the usual Brønsted–Bjerrum salt-effect equations. Indeed he showed experimentally that the kinetic expressions (F)

$$k = \text{Const.} \times h_0 \text{ and } \log_{10} k = -H_0 + \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad (F)$$

could often replace the ideal equation $k = \text{Const.} \times [H^+]$ which holds satisfactorily for very dilute solutions only.

Fig. 3, in which Hammett's acidity function H_0 for aqueous sulphuric acid (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827) has been plotted against $\log_{10} k_{\text{observed}}$ for the sulphuric-acid-catalysed bromination, shows that his velocity relationship (F) holds at low acidities, when $k_{\text{obs.}}$ is approximately constant, but that at higher acidities k_{observed} increases rather more rapidly, since $\log_{10} k_{\text{observed}}$ becomes a linear function of H_0 with a gradient of $-1{\cdot}7$ instead of the expected value of $-1{\cdot}0$. It is improbable that this discrepancy can be due to the use of 40% acetic acid as the solvent, since Paul and Hammett (*ibid.*, 1936, **58**, 2182) have reported that H_0 for sulphuric acid is almost the same in 50% acetic acid as in water. A similar positive deviation of substitution rates from acidity functions has been noted for aromatic nitrations in 80—90% sulphuric acid (Gillespie and Millen, *loc. cit.*).

Now for the bromination of undissociated benzoic acid we may write (G):

$$k_{\text{obs.}}[\text{Benz}][\text{HOBr}] = Kk_2[\text{HOBr}][\text{H}^+][\text{Benz}]\left\{\frac{f_{\text{HOBr}} \cdot f_{\text{H}^+} \cdot f_{\text{Benz}}}{f_{\ddagger}}\right\} \quad . \quad . \quad \text{(G)}$$

and hence

$$k_{\text{observed}} = Kk_2[\text{H}^+]\left\{\frac{f_{\text{H}^+} \cdot f_{\text{HOBr}}}{f_{\text{H}_2\text{OBr}^+}}\right\} \times \left\{\frac{f_{\text{H}_2\text{OBr}^+} \cdot f_{\text{Benz.}}}{f_{\ddagger}}\right\} \quad . \quad . \quad . \quad . \quad \text{(H)}$$

If Hammett's acidity function hypothesis is to be followed, then we should compare the activity factor $\left\{\frac{f_{\text{H}^+} \cdot f_{\text{HOBr}}}{f_{\text{H}_2\text{OBr}^+}}\right\}$ with the expression $\left\{\frac{f_{\text{H}^+} \cdot f_{\text{I}}}{f_{\text{HI}^+}}\right\}$ for an indicator system, since equilibrium (1*b*) is exactly that corresponding to a weakly basic indicator. Equation (H) above, however, shows clearly that the bromination which we have studied depends also on the ensuing chemical reaction between the $(H_2OBr)^+$ cation and the benzoic acid molecule, and for this reaction the further activity factor product $\left\{\frac{f_{\text{H}_2\text{OBr}^+} \cdot f_{\text{Benz.}}}{f_{\ddagger}}\right\}$ must be taken into account. Since high concentrations of ions and molecules are involved it would be expected that our reaction should exhibit a positive *linear* salt effect (cf. R. P. Bell, *op. cit.*; Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," p. 62, New York, 1941) ascribable to the net value of the activity-coefficient expression given immediately above. The extended Debye–Hückel theory would then lead to the expression (I)

$$\log_{10} k_{\text{observed}} = -H_0 + B\mu + \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(I)}$$

and since at high acid concentrations H_0 becomes nearly a linear function of the mineral acid concentration (Hammett and colleagues, *loc. cit.*) the "salt effect" represented by the term $B\mu$ in equation (I) may be written as bH_0. Equation (I) then reduces to (J)

$$\log_{10} k_{\text{observed}} = -(1 + b)H_0 + \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(J)}$$

and in this way the shape of the graphical results of Fig. 3 becomes explicable. This theoretical approach is however far too approximate for any attempt at quantitative treatment.

Table II shows that neutral salts still further increase the rate of bromination of benzoic acid in both sulphuric and perchloric acid. This may be due both to the positive salt effect discussed above and to the effect of neutral salts on the acidity function H_0 (Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 828).

TABLE II.

The effect of neutral salts on the bromination of benzoic acid by bromine cations at 21·5°.

Acid.	Salt added.	$k_{\text{bi.}}$ (found).
H_2SO_4 0·294M.	—	0·01626 mol./l./sec.
H_2SO_4 0·294M.	$NaNO_3$ 1·3M.	0·0689 "
$HClO_4$ 0·448M.	—	0·036 "
$HClO_4$ 0·448M.	$NaClO_4$ 0·448M.	0·0547 "
$HClO_4$ 0·224M.	—	0·012 "
$HClO_4$ 0·224M.	$NaClO_4$ 0·672M.	0·0242 "

In the concentration range which we have used, the acidity functions for sulphuric and perchloric acids are almost identical. The slight deviation in the catalytic reactivities of these two acids may perhaps be due to the intervention of the equilibrium (5)

$$(\text{H}_2\text{OBr})^+ + (\text{SO}_4)^{--} \rightleftharpoons (\text{SO}_3\text{Br})^- + \text{H}_2\text{O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(5)}$$

since the second dissociation constant of sulphuric acid is low enough for the $(SO_4)^{--}$ anion to function as a base. From the relevant equations for the equilibria concerned, it is easily possible to derive the expression (K)

$$[SO_4Br^-] = \text{Const. } [HOBr][HSO_4^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (K)$$

which is similar to those used by Mauger and Soper (*loc. cit.*) in considering the effects of buffers on certain substitution reactions of hypochlorous acid. From equation (K) it can be seen that there should be an increasing conversion of highly active $(H_2OBr)^+$ cations into inactive $(SO_4Br)^-$ as the concentration of the sulphuric acid is increased, though this should not be an effect of the same order as the increasing conversion of neutral HOBr into $(H_2OBr)^+$.

The Relative Reactivities of Hypobromous Acid and Molecular Bromine.—The foregoing work has shown that the relative rates of bromination by means of molecular hypobromous acid and molecular bromine cannot be compared in appreciably acid solution. To confirm the correctness of the polarity theory of Ingold, we have made a direct comparison of the relative

FIG. 3.

Relationship between $\log k_{bi.}$ *and Hammett's acidity function* H_0 *for the bromination of benzoic acid with a sulphuric acid catalyst.*

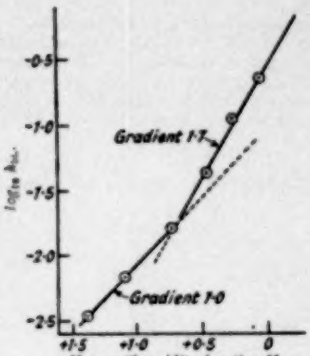
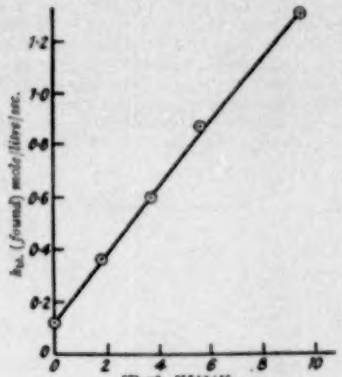


FIG. 4.

Bromination of sodium p-anisate with hypobromous acid/bromine mixtures at pH 7·58.



velocities of substitution of sodium *p*-anisate by these two substances in dilute solutions in phosphate buffers in the range pH 7—8, *i.e.*, in circumstances in which hypobromous acid ($K_a = 2{\cdot}06 \times 10^{-8}$) (cf. Shilov and Gladtchikova, *J. Amer. Chem. Soc.*, 1938, **60**, 490) would be undissociated and the aromatic substrate present as the anion. At pH 7·6 hypobromous acid gradually decomposes giving some free bromine, and so when it was used in homogeneous solution the rate of substitution was found to rise after a time. However, by working with a rapidly shaken solution containing suspended silver phosphate it was possible to obtain good second-order velocity constants until more than 75% of the material had been used; these constants corresponded to the initial velocity of the reaction in a similar solution containing no silver phosphate, which therefore acts only to regenerate hypobromous acid from aqueous bromine.

Bromine itself reacts far too rapidly with sodium *p*-anisate for it to be possible to obtain accurate velocity constants, but convincing results were obtained by adding small quantities of potassium bromide to the homogeneous hypobromous acid solutions, when, as our observations show, the equilibrium (6) is set up instantaneously. If we assume

$$HOBr + Br^- + H^+ \underset{K_{hyd.}}{\rightleftharpoons} Br_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

that this is true, and that hypobromous acid and bromine substitute concurrently, and remember that they can be titrated in exactly the same way, we can write (L):

$$\text{Velocity of substitution} = k_{bi}[\text{HOBr}][\text{Ar}^-]$$
$$= k_{\text{HOBr}}[\text{HOBr}][\text{Ar}^-] + k_{\text{Br}_2}[\text{Br}_2][\text{Ar}^-]$$
$$= [\text{HOBr}][\text{Ar}^-]\{k_{\text{HOBr}} + k_{\text{Br}_2}[\text{Br}^-][\text{H}^+]/K_{hyd.}\} \quad . \quad . \quad . \quad . \quad (\text{I.})$$

where $K_{hyd.} = [\text{Br}^-][\text{H}^+][\text{HOBr}]/[\text{Br}_2]$, the equilibrium constant for (6). The latter has been calculated as $4{\cdot}29 \times 10^{-9}$ at the temperature used (21·5°) from the equation given by Liebhafsky (*J. Amer. Chem. Soc.*, **1934**, **56**, 1500; **1939**, **61**, 3513).

Now substitution of an aromatic nucleus by hypobromous acid does not affect the acidity of the solution, and the reaction (7)

$$\text{Br}_2 + \text{MeO·C}_6\text{H}_4\text{·CO}_2^- \longrightarrow \text{Br}^- + \text{H}^+ + \text{MeO·C}_6\text{H}_3\text{Br·CO}_2^- \quad . \quad . \quad . \quad (7)$$

(i) regenerates bromide anions as the free bromine is consumed and (ii) reproduces the hydrogen ions used up in the formation of molecular bromine (equation 6), so that in our reaction system both $[\text{Br}^-]$ and $[\text{H}^+]$ remain constant. Consequently, as Fig. 4 shows, the graph of k_{bi} against the function $[\text{Br}^-][\text{H}^+]/K_{hyd.}$ gives a linear plot, from the slope of which k_{Br_2} has been evaluated as 119 mole/l./sec.

The data plotted on Fig. 4 give the ratio $k_{\text{HOBr}} : k_{\text{Br}_2}$ as 1 : 1100, and an approximate ratio of this order was also obtained in attempt to measure k_{Br_2} directly in an identical buffer solution.

However the figure for k_{HOBr} derived from the data of Fig. 4 is itself that for a composite velocity constant. Lines 1—4 of Table III show that as the normality of the phosphate buffer is increased the velocity of bromination of sodium *p*-anisoate (without added bromide) increases also, though the pH of the solution has not changed. On the other hand comparisons between lines 2*a* and 2*b*, and between lines 3*a* and 3*b* of Table III show that if the acid component of the buffer is kept in constant concentration, then, although the pH of the reacting mixture may vary in the range of pH 7—8 which does not sensibly affect the dissociation of molecular hypobromous acid, the velocity of bromination remains nearly constant.

TABLE III.

Bromination of sodium p-*anisate with bromine-free hypobromous acid in phosphate buffers at* 21·5°.

	Na_2HPO_4, M., $\times 10^{-3}$.	KH_2PO_4, M., $\times 10^{-3}$.	pH (glass electrode).	HOBr, M., $\times 10^{-9}$.	Anisate, M., $\times 10^{-3}$.	k_{bi} (found), mol./l./sec.
2*a*	1·13	2·00	7·58	4·23	7·03	0·105
1	1·13	2·00	7·58	5·04	14·06	0·112
2*b*	2·99	2·00	7·92	4·29	7·03	0·103
3*a*	3·26	4·00	7·58	4·29	7·03	0·161
3*b*	1·13	4·00	7·40	4·21	7·03	0·166
4	3·39	6·00	7·58	3·99	7·03	0·221
	No buffer salt		7·58	By extrapolation $k_{bi} = 0{\cdot}05$		

These results can be explained, in accordance with the views of Mauger and Soper (*loc. cit.*), by supposing that there can be formed a bromine phosphate which is somewhat more reactive than undissociated hypobromous acid. Thus a change in the potassium dihydrogen phosphate concentration shifts the equilibrium (8), whilst a change of the pH at constant $[\text{H}_2\text{PO}_4^-]$

$$\text{HOBr} + \text{H}_2\text{PO}_4^- \rightleftharpoons (\text{Br·HPO}_4)^- + \text{H}_2\text{O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

does not. The second dissociation constant for phosphoric acid ($K_a = 6 \times 10^{-8}$) is much greater than the dissociation constant for water, and this sequence therefore accords with Ingold's views on the relative reactivities of compounds Br—X.

The extrapolation of the experimental results of Table III shows that the value of k_{HOBr} for the bromination of sodium *p*-anisate in the absence of any buffer is of the order of 1/2000 of the value of k_{Br_2} computed from the data given in Fig. 4. This ratio is about double that of the previous estimates of Francis and of Shilov and Kaniaev, neither of whom however took such careful precautions to eliminate either effects due to acidity or effects due to small traces of free bromine.

The results of the first part of this paper show conclusively that the bromine cation is very much more reactive than molecular bromine, but since the value of the equilibrium constant for the system (1*b*) is unknown we cannot express in figures the relative reactivities of molecular and kationic bromine. Alexander (*loc. cit.*) has ascribed an appreciable brominating power to the complex anion $(\text{Br}_3)^-$. On the other hand, Bradfield, Davies, and Long (*J.*, **1949**, 1393)

have shown that $(Br_3)^-$ is a much less active brominating agent than either hypobromous acid or molecular bromine; the same conclusion was reached for bromine addition by Bartlett and Tarbell (*loc. cit.*). Our results show that the ion $(Br_3)^-$ cannot play an appreciable part in the bromination of sodium *p*-anisate under our conditions of reaction, for if a concurrent substitution by this ion were concerned then the reaction velocity equation (I.) (p. 570) would have to include a term

$$k_{Br_3^-} \cdot \frac{[Br^-]^3 \cdot [H^+]}{K_{Br_3^-} \cdot K_{hyd}}$$

which is of second order with respect to $[Br^-]$.

The theoretical curve for Fig. 4 would then become parabolic and not linear. The linearity of the results plotted in Fig. 4 therefore establishes that at pH 7—8 the most active brominating agent present in aqueous solutions is the simple bromine molecule, Br_2. At this acidity the concentration of the bromine cation (Br^+ or H_2OBr^+) must be quite insignificant because the substitution of sodium *p*-anisoate is not pH-dependent in slightly alkaline solution. Again, addition of bromide anion cannot in any way increase the concentration of the bromine cation in the equilibrated system (I) (p. 565), yet it does most markedly increase the rate of aromatic substitution.

Finally we would point out that in polar solvents the substitution reaction of *N*-halogeno-compounds may often be due to the formation of similar systems of cationoid reactivity (*e.g.*, 9).

$$R_2N{-}Br + H^+ \rightleftharpoons (R_2NH{-}Br)^+ \rightleftharpoons R_2NH + Br^+ \quad . \quad . \quad . \quad . \quad (9)$$

Schmid (*Helv. Chim. Acta*, 1946, **29**, 1144) for instance has found that *N*-bromosuccinimide can be used to substitute benzene and toluene in the presence of concentrated sulphuric acid. The molecular rearrangements and aromatic substitutions which can be effected by *N*-chloro- and *N*-bromo-compounds are again reactions which proceed *via* their conjugate acids, since they are dependent on general acid catalysis.

Experimental.

Hypobromous Acid.—Aqueous solutions of hypobromous acid were prepared by the method of Shilov and Kaniaev (*J. Gen. Chem. Russia*, 1938, **8**, 445, in Russian) by shaking *ca.* 0·08*N*-bromine-water, made from purified bromine, b. p. 58·1°/747 mm., with an excess of freshly prepared silver phosphate. When the smell of free bromine had disappeared (1 hour), the resulting solution was distilled from a water-bath at 40—50° under a water-pump vacuum, in an all-glass apparatus the outside of which had been covered with a heavy coat of black paint to exclude light. The condenser and receiver were both cooled in ice-water, and the latter was protected by a trap to avoid back-diffusion of impurities arising from interactions of hypobromous acid and rubber connections. The hypobromous acid solutions thus obtained were about 0·02M. and had a very pale yellow colour, most of which was due to the presence of traces of free bromine. Nearly all the latter was then removed by extracting the distillate at 0—5° with carbon disulphide-free carbon tetrachloride, and the last traces of the extractant were eliminated by centrifugation. Solutions of hypobromous acid prepared in this way give no precipitate with silver nitrate, though on storage an opalescence gradually develops. Analyses, carried out as described below, show that the product may still contain up to 2% of free bromine, but that it is almost free from bromic acid. It is reasonably stable at 0°, but, when frozen so that ice separates and the remaining liquid becomes much more concentrated, extensive decomposition occurs. Aqueous solutions which have been diluted to about 5×10^{-3}M. can be kept for about an hour at summer temperatures (20—25°) without exhibiting any change in titre or noticeable increase in free bromine content.

For the kinetic work these solutions were regularly analysed by the following methods, and allowance was made for the presence of free bromine, after it had been established that this did not react with either benzoic acid or sodium toluene-ω-sulphonate in the aqueous mixtures used.

Analytical Methods.—(i) ($HOBr + Br_2 + HBrO_3$) was determined by addition to potassium iodide in dilute sulphuric acid solution followed by thiosulphate titration. (ii) Br_2 was estimated by difference, since it did not react with benzoic acid even in strong sulphuric acid solution. 5 Ml. of the hypobromous acid reagent were run into 20 ml. of a solution of 1 g. of benzoic acid in a mixture of 40 ml. each of stabilised glacial acetic and 10*N*-sulphuric acids in a stoppered flask. After 6 minutes, when the HOBr had reacted completely, aliquots of this solution were run into aqueous potassium iodide, and titrated with thiosulphate. (iii) $HBrO_3$ was determined also by difference, by use of an excess of aqueous crotonic acid to remove both HOBr and Br_2, as indicated by Shilov and Kaniaev. The remaining $HBrO_3$ was allowed to liberate iodine from potassium iodide in strong hydrochloric acid in the presence of a few drops of ammonium molybdate solution, added as a catalyst. A typical analysis gave the values: HOBr, 0·018M.; Br_2, 5×10^{-4}M.; $HBrO_3$ under 4×10^{-4}M.

Quantitative Bromination of Sodium Toluene-ω-sulphonate.—Sodium toluene-ω-sulphonate (Fromm and Seixas Palma, *Ber.*, 1906, **39**, 3309) was crystallised first from hot water and then from absolute alcohol, and finally dried in a vacuum at 100°. It was neutral, stable to cold permanganate solution, and gave no precipitate with silver nitrate or barium chloride solutions. A stock solution in distilled water was mixed as required with standardised perchloric acid prepared from AnalaR chloride-free

material. For kinetic measurements, freshly prepared dilute hypobromous acid was added to the prepared samples of the acidified aromatic compound contained in blackened glass-stoppered flasks immersed in a thermostat at 21·5° ± 0·05°, the initial volume regularly being 50 ml. At intervals, 5-ml. portions were withdrawn for titration with N/100-thiosulphate, by a semi-micro-burette. Since the temperature of the thermostat was very close to that of the laboratory the time of reaction could be measured to as high a degree of accuracy as that of half-addition of the mixtures to acidified potassium iodide solution. Immediately after each experiment the purity of the hypobromous acid solution was checked.

The examples in Table IV show the accuracy of the determinations of the second-order reaction velocity coefficient.

TABLE IV.

Bromination of sodium toluene-α-sulphonate with hypobromous acid.

(*A*) $Ph{\cdot}CH_2{\cdot}SO_3Na$ = 7·09 × 10^{-3}M., HOBr = 4·73 × 10^{-3}M., $HClO_4$ = 0·0942N.

Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.
0	0	4·59	100	—
0	37	3·37	73·5	1·306
1	11	2·68	58·4	1·263
2	10	1·89	41·2	1·268
3	58	1·10	24·0	1·286
6	2	0·66	14·4	1·279
8	20	0·41	8·9	1·154

Mean $k_{bi.}$ = 1·275 ± 0·03 mole/litre/sec.

(*B*) $Ph{\cdot}CH_2{\cdot}SO_3Na$ = 7·09 × 10^{-3}M., HOBr = 4·079 × 10^{-3}M., $HClO_4$ = 0·00942N.

Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.
0	0	3·96	100	—
0	58	3·73	94·2	0·1477
3	15	3·26	82·3	0·1479
5	41	2·88	72·7	0·1440
8	43	2·46	62·1	0·1460
15	21	1·83	46·3	0·1448
25	25	1·23	31·1	0·1446

Mean $k_{bi.}$ = 0·146 ± 0·002 mol./litre/sec.

Quantitative Bromination of Benzoic Acid.—AnalaR benzoic acid was dissolved in purified acetic acid (Orton and Bradfield, *J.*, 1924, **125**, 960), and the solutions were diluted with the chosen specimens of dilute sulphuric or perchloric acids so that the final mixture contained 40% of acetic acid by volume. Velocity measurements were conducted at 21·5° by the procedure described above. The examples in Table V show that the bromination is strictly a second-order reaction.

TABLE V.

Bromination of benzoic acid with hypobromous acid.

(*A*) $Ph{\cdot}CO_2H$ = 7·876 × 10^{-3}M., HOBr = 3·747 × 10^{-3}M., H_2SO_4 = 2·352N.

Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.
0	0	3·92	100	—
1	18	3·38	86·2	0·2503
4	35	2·44	62·2	0·2432
8	56	1·59	40·6	0·2577
12	18	1·20	30·6	0·2568
17	21	0·80	20·2	0·2580
24	14	0·48	12·2	0·2590
33	11	0·26	6·6	0·2586

Mean $k_{bi.}$ = 0·255 ± 0·004 mole/litre/sec.

(*B*) $Ph{\cdot}CO_2H$ = 7·876 × 10^{-3}M., HOBr = 4·035 × 10^{-3}M., $HClO_4$ = 0·1176N.

Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.
0	0	4·14	100	—
8	12	3·43	82·8	0·00487
15	1	2·89	69·8	0·00511
20	58	2·51	60·6	0·00511
29	7	2·07	50·0	0·00511
37	43	1·69	40·8	0·00512
47	29	1·36	32·8	0·00507

Bromination of Sodium p-*Anisate with Hypobromous Acid.*—Hypobromous acid, prepared as described above, was shaken with freshly prepared silver phosphate at 0° for 4 hours, filtered through sintered glass, and added to a buffered solution of sodium *p*-anisate maintained at 21·5° in a thermostat. Table VI indicates the ensuing rate of reaction. The pH given was determined by means of a glass electrode standardised against pure potassium hydrogen phthalate.

TABLE VI.

Reaction of hypobromous acid with sodium p-*anisate at* pH 7·58.

MeO·C_6H_4·CO_2Na = 7·03 × 10^{-3}M., HOBr = 4·20 × 10^{-3}M.

Na_2HPO_4 = 0·0113M. } Buffer pH = 7·58.
KH_2PO_4 = 0·0020M. }

Time: min.	sec.	Titre (corr. for Br_2), ml.	k (bimol.), calc.	Time: min.	sec.	Titre (corr. for Br_2), ml.	k (bimol.), calc.
0	0	4·15	—	12	19	1·96	0·1776
4	10	3·45	0·1105	17	5	1·36	0·2075
8	27	2·58	0·1529	22	0	0·94	0·2339

Since solutions of hypobromous acid when stored at pH 7—8 in the absence of the aromatic reactant gradually developed a yellow colour, this increase in $k_{bi.}$ was ascribed to the slow formation of free bromine. To obviate this, a similar mixture containing silver phosphate still in suspension was

agitated mechanically whilst the bromination with sodium *p*-anisate was carried out. Under these conditions the result recorded in Table VII was obtained.

TABLE VII.

Reaction of hypobromous acid with sodium p-*anisate in presence of solid silver phosphate at* pH 7·58; *temp.* 21·5°.

$MeO{\cdot}C_6H_4{\cdot}CO_2Na = 1{\cdot}406 \times 10^{-4}$M., HOBr = $5{\cdot}043 \times 10^{-4}$M. $Na_2HPO_4 = 0{\cdot}0113$M., $KH_2PO_4 = 0{\cdot}0020$M. } Buffer pH = 7·58.

Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.	Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.) calc.
0	0	4·98	100	—	8	59	2·33	46·8	0·1127
2	1	4·08	81·9	0·1212	12	52	1·78	35·7	0·1101
4	10	3·41	68·5	0·1148	17	30	1·20	24·1	0·1100
6	7	2·89	58·0	0·1150					

Mean $k_{bi.} = 0{\cdot}113 \pm 0{\cdot}003$ mole/litre/sec.

In subsequent experiments, in which potassium bromide was added to the reaction mixtures to provide a low, but constant, concentration of bromide anions, filtered hypobromous acid solutions were used. The extrapolation of the results so obtained (cf. Fig. 4) confirms the validity of the result given in Table VII and indicates that heterogeneous catalysis does not intervene.

Table VIII indicates typical results obtained in the presence of low concentrations of bromide anions.

TABLE VIII.

Bromination of sodium p-*anisate with a hypobromous acid–bromine mixture at* pH 7·58; *temp.* 21·5°.

$MeO{\cdot}C_6H_4{\cdot}CO_2Na = 7{\cdot}03 \times 10^{-4}$M., HOBr = $4{\cdot}355 \times 10^{-4}$M., KBr = $1{\cdot}08 \times 10^{-2}$M. $Na_2HPO_4 = 0{\cdot}0113$M., $KH_2PO_4 = 0{\cdot}002$M. } Buffer pH = 7·58 (glass electrode).

Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.	Time: min.	sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %	k (bimol.), calc.
0	0	4·30	100	—	3	3	1·28	31·0	1·308
0	38	3·12	75·6	1·323	4	7	0·92	22·3	1·323
1	13	2·44	59·1	1·304	5	42	0·59	14·3	1·336
2	3	1·80	43·6	1·289	7	50	0·34	8·2	1·346

Mean $k_{bi.} = 1{\cdot}32 \pm 0{\cdot}02$ mole/litre/sec.

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, October 31st,* 1949.]

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108. *The Significance of the Bromine Cation in Aromatic Substitution. Part II. Preparative Applicability.*

By D. H. DERBYSHIRE and WILLIAM A. WATERS.

Acid solutions of hypobromous acid contain a very much higher concentration of bromine cations than do acid solutions of free bromine. Highly reactive solutions containing bromine cations can be made by adding mercuric or silver salts gradually to solutions of bromine in water or acetic acid in the presence of either nitric or sulphuric acid. Benzene, chlorobenzene, bromobenzene, and *p*-dibromobenzene can be brominated with such mixtures in 2N-nitric acid; benzoic acid and methyl benzoate require a stronger nitric acid solution, whilst nitrobenzene, 2 : 4-dinitrotoluene, and *m*-dinitrobenzene need 90% sulphuric acid. The expected aromatic bromination products have been isolated from these substances in 60—80% yield.

Bromine cations can also be formed by adding potassium bromate to acid solutions of bromine, and these mixtures too constitute active brominating agents.

Acetic and propionic acids, methyl alcohol, and dioxan all resist attack by bromine cations in 2N-mineral acid.

The experimental evidence substantiates the polar-activation theory of aromatic substitution.

THE kinetic evidence given in Part I (preceding paper) shows that hypobromous acid becomes a powerful brominating agent in the presence of mineral acid owing to the production of bromine cations (I),

$$H^+ + HOBr \overset{K}{\rightleftharpoons} (H_2OBr)^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

and the present paper indicates the importance of this equilibrium in preparative chemistry and gives examples of its applications.

The preparation of free hypobromous acid requires such care that the reagent as such cannot conveniently be used in quantity, and, as the following calculations show, only exceedingly minute concentrations of bromine cations can be present in aqueous solutions of free bromine.

The equilibrium constant for bromine hydrolysis (2) has the low value of $4{\cdot}7 \times 10^{-9}$ at room temperature (Liebhafsky, *J. Amer. Chem. Soc.*, 1934, **56**, 1500), and consequently the

$$H_2O + Br_2 \underset{K_{hyd.}}{\rightleftharpoons} HOBr + H^+ + Br^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

degree of hydrolysis α of a bromine solution of concentration C in a medium of acidity $[H^+]$ is given by the relation

$$[\alpha^2C^2[H^+]/C(1 - \alpha) = 4{\cdot}7 \times 10^{-9}$$

whence, writing $[H_2OBr^+] = K[H^+][HOBr]$ and remembering that α is small in acid solutions, we can deduce that

$$[H_2OBr^+] = \frac{\alpha C[H^+]}{K} = \text{approx. } \frac{7 \times 10^{-9}}{K}\sqrt{C[H^+]}$$

whilst for equivalent solutions of hypobromous acid

$$[H_2OBr^+] = C[H^+]/K$$

For N/10-solutions these two concentrations of bromine cations differ by an order of 10^4 in N-acid, and become comparable only under conditions approaching neutrality (pH *ca.* 6) in which α increases. However, in these neutral solutions $[H_2OBr^+]$ is so minute that reactions due to bromine cations can no longer be clearly detected (compare the bromination of sodium toluene-ω-sulphonate and of sodium *p*-anisate studied in Part I).

However in acid media one can easily carry out brominations by means of bromine cations by adopting the simple procedure of adding to a bromine solution a further reagent which is capable of removing bromide anions from the system. For example, if silver nitrate is added to an aqueous bromine solution then, since the solubility product of silver bromide is $7{\cdot}7 \times 10^{-13}$ at 25°, the conversion of bromine into hypobromous acid, *via* the hydrolysis (2), is so complete that we may write

$$[H_2OBr^+] = [H^+][HOBr]/K = [H^+]([Ag^+] \text{ added})/K$$

Mercuric salts can be used in the same way, and since mercuric bromide, though un-ionised in acid media, is soluble in water the following simple experiments may be conducted to demonstrate the production and reactivity of bromine cations.

A little bromine water is added to an aqueous solution of benzene in each of two vessels. (i) To one sample dilute nitric acid is added; the solution remains of a clear orange colour. (ii) To a second sample dilute mercuric nitrate solution is added; the colour almost vanishes owing to the conversion of bromine into inactive hypobromous acid. (iii) Sample (ii) is then treated dropwise with dilute nitric acid; the bromine colour begins to reappear and the mixture soon becomes turbid owing to the separation of droplets of bromobenzene. As the reaction proceeds the colour becomes fainter again. (iv) When the acidified sample (i) is treated with mercuric nitrate solution, the bromine colour fades and droplets of bromobenzene separate.

On the preparative scale we have found that benzene can be converted into bromobenzene in 80% yield by adding silver nitrate solution dropwise to a stirred emulsion of benzene in 2N-nitric acid containing bromine. The 20% loss in yield is due to the formation of dibromobenzene. Mercuric nitrate gave a 70% yield, but the separation of the product was rather more difficult, since mercuric bromide is both slightly soluble in ether and slightly volatile. Lead nitrate was useful only for rather more reactive substances such as toluene: lead bromide is decidedly more soluble than silver bromide.

Aromatic substances which are very insoluble in water can be brominated in a similar way by using aqueous acetic acid containing either nitric or sulphuric acid. In this way we have successfully brominated chlorobenzene, bromobenzene, *p*-dibromobenzene, benzoic acid, and methyl benzoate, and have isolated in high yield the expected products of their cationoid aromatic substitution. Inactive *meta*-substituting substances, such as nitrobenzene, *m*-dinitrobenzene, and 2 : 4-dinitrotoluene do not react appreciably with the low concentrations of bromine cations that are present in 1—2N-acid, but they can all be brominated very effectively in 90% sulphuric acid by the use of silver sulphate.

Silver sulphate is soluble in concentrated sulphuric acid, and when bromine is added to such a solution the mixture merely becomes opalescent, presumably because the acidity of the solution has diminished the hydrolysis of bromine so much that the solubility product of silver bromide is not greatly exceeded. When, however, the aromatic compound is added to this mixture, silver bromide is steadily deposited as the bromination proceeds. Evidently the removal of hypobromous acid, *via* $(H_3OBr)^+$, increases the bromide anion concentration so that silver bromide can be precipitated, and this simultaneous removal of both $(H_3OBr)^+$ and (Br^-) allows the complete reaction with bromine to be effected. With *m*-dinitrobenzene however heating to 100° was necessary. In the absence of silver sulphate these inactive nitro-compounds do not react, even at 100°, with bromine in 90% sulphuric acid, but when it is added the expected bromo-derivative can easily be prepared in 60—80% yield.

Since no other method of bromination of these deactivated aromatic compounds, such as heating to a high temperature with an iron catalyst, gives comparable yields of clean material it is evident that free bromine cations must have an extremely high degree of reactivity. Nevertheless pyridine sulphate withstood attack under our conditions at 100°. It is possible that the free ion Br^+ rather than the solvated ion $(H_3OBr)^+$ may be present in these concentrated acid solutions, but we have not attempted as yet to discriminate between them. This direct experimental proof that the bromine cation will attack substances such as benzoic acid and nitrobenzene which are not attacked by molecular bromine substantiates the theory that the catalysts normally used to effect aromatic bromination do so by polar activation, *e.g.*, $Br_2 + FeBr_3 \rightleftharpoons (Br^+)(FeBr_4^-)$; their lower efficacy may perhaps indicate that ion-pairs rather than *free* bromine cations are often formed. Hence the major advantage of our new procedure may lie in the fact that the bromine cations are formed in solution and not on the surface of a solid catalyst.

The physical principle of effecting cationoid bromination by removing bromide anions from an acid solution of bromine can be applied practically in other ways than those described above. For instance in 1875 Krafft (*Ber.*, 1875, **8**, 1045) noted that a mixture of bromine with potassium bromate in 33% sulphuric acid constituted a brominating agent which would readily brominate both benzene and bromobenzene at room temperature, and we have confirmed that bromine–bromate mixtures are very effective in 50% sulphuric acid. The rôle of the bromate is clearly the removal of bromide anions

$$5H^+ + 5Br^- + HBrO_3 \rightleftharpoons 3H_2O + 3Br_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and from the equilibria (1), (2), and (3) can be derived the relation

$$[H_3OBr]^+ = \text{Const.}\ [H^+][Br_2]^{\frac{1}{2}}[HBrO_3]^{\frac{1}{2}}$$

which indicates that even small concentrations of bromates should be exceedingly effective as catalysts.

It is interesting to note that the direct iodination of nitrobenzene has been effected by Masson and Hanby (*J.*, 1938, 1699) by the use of a very similar system in which they considered that iodine cations were present. Many other similar reaction mixtures for the preparation and study of the reactive cations of the halogens can now be envisaged.

It may be noted that we have, as yet, effected only the cationoid bromination of aromatic nuclei; alkyl side-chains, as in 2 : 4-dinitrotoluene, do appear not to be attacked. Though we have not attempted to carry out the cationoid bromination of saturated aliphatic molecules in concentrated sulphuric acid we have found that carefully purified specimens of acetic acid, propionic acid, methyl alcohol, and dioxan were all quite unaffected by hypobromous acid in 2*N*-sulphuric acid solution. In each case the drop in titre of the hypobromous acid was not detectable after an hour at 22·4°. This would appear to be a significant indication that the reaction (4) does not normally occur in aqueous solution, although it conflicts with the recent

$$H_2OBr^+ + R_3C{-}H \longrightarrow Br{-}CR_3 + H_2O^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

demonstration by Arcus, Campbell, and Kenyon (*J.*, 1949, 1510) that a Walden inversion can be brought about by an analogous exchange of ions in carbon tetrachloride solution. The discrepancy may perhaps be due to the solvation of the bromine cation and the stabilising effect of the ionising solvent on the substitution reaction as a whole.

Experimental.

Bromination of Benzene.—Benzene (22 ml., 0·25 mol.) and bromine (6·5 ml., 0·125 mol.) were stirred together in 1 l. of 2*N*-nitric acid, and 22 g. (0·125 mol.) of silver nitrate in water (100 ml.) were added gradually during 1½ hours. Light was excluded from the reaction mixture. After removal of residual

bromine by sodium sulphite the product was extracted with ether, dried, and fractionated. It gave 15 g. (80% calc. on the bromine) of pure bromobenzene. Rapid addition of the silver nitrate diminished the yield and produced more dibromobenzene. In the absence of silver nitrate there was no reaction.

Brominations of Chlorobenzene, Bromobenzene, and p-Dibromobenzene.—Chlorobenzene (12 ml., 0·1 mol.) and bromine (5·2 ml., 0·1 mol.) were dissolved in a mixture of glacial acetic acid (300 ml.) and diluted nitric acid [50 ml. (*d* 1·4) in 100 ml. of water]. To the stirred cold mixture, silver nitrate solution (17 g. in 50 ml. of water) was added dropwise during ½ hour. The resulting solution was diluted with water (2 l.), freed from residual bromine, partly neutralised and extracted with ether. The dried extract was fractionated and the resulting *p*-chlorobromobenzene crystallised from alcohol; yield, 11 g.; m. p. 65—67°.

Bromobenzene (17 g.) was treated similarly and gave 13 g. of *p*-dibromobenzene, of m. p. and mixed m. p. 85—86°. *p*-Dibromobenzene (12 g.) was brominated similarly in a mixture of 700 ml. of acetic acid, 65 ml. of nitric acid (*d* 1·4), and 50 ml. of water at 40°. The reaction product contained an involatile residue which was separated by fractional crystallisation from ethyl alcohol into 1 : 2 : 4-tribromobenzene, m. p. 42—44°, and 1 : 2 : 4 : 5-tetrabromobenzene, m. p. 177—178°.

Bromination of Benzoic Acid and Methyl Benzoate.—Benzoic acid (13 g., 0·1 mol.) and bromine (5·2 ml., 0·1 mol.) were dissolved in a mixture of glacial acetic acid (300 ml.), concentrated nitric acid (65 ml.), and water (50 ml.), and treated dropwise, with vigorous mechanical stirring, with aqueous silver nitrate (17 g. in 100 ml. of water). The resulting solution yielded 14 g. of *m*-bromobenzoic acid, m. p. 152—154°. Methyl benzoate (16 g.) was treated similarly and the product was distilled under reduced pressure; it gave 7 g. of methyl *m*-bromobenzoate, b. p. 117—120°/20 mm., m. p. 28—30°.

Bromination of Nitrobenzene and 2 : 4-Dinitrotoluene.—Nitrobenzene (10 ml., 0·1 mol.) and bromine (5·2 ml., 0·1 mol.) were dissolved in a mixture of 90 ml. of concentrated sulphuric acid and 10 ml. of water, and silver sulphate (17 g., 0·1 mol.) was then added. The mixture was shaken mechanically for 16 hours, after which time the colour of the bromine had almost disappeared and silver bromide had been precipitated. The resulting solution was diluted with water, freed from remaining bromine, and extracted with ether. The dried extract solidified on cooling and gave 14·8 g. (70%) of *m*-bromonitrobenzene, m. p. and mixed m. p. 55—56°.

2 : 4-Dinitrotoluene (18·5 g., 0·1 mol.) was brominated in a similar manner during 36 hours and gave 16 g. (80%) of *6-bromo-2 : 4-dinitrotoluene* which crystallised from alcohol in long pale yellow needles, m. p. 57·5—58° (Found: N, 10·6. $C_7H_5O_4N_2Br$ requires N, 10·7%). These became deep yellow on prolonged exposure to sunlight and gave a very intense reddish-purple colour when treated with acetone and aqueous potassium hydroxide. The compound was not hydrolysed when refluxed with alcoholic potassium hydroxide, and hence the bromine is neither adjacent to a nitro-group nor in the side-chain.

Bromination of m-Dinitrobenzene.—*m*-Dinitrobenzene (8·5 g., 0·05 mol.), bromine (3 ml.), and silver sulphate (8 g.) were dissolved in concentrated sulphuric acid (100 ml.). The mixture was left overnight without the onset of reaction; it was then heated under a reflux at 100° for 11 hours, during which silver bromide was steadily deposited. The resulting solution, after dilution with water, yielded 6·5 g. of a solid organic product which, after repeated crystallisation from alcohol, gave 5·5 g. of 1-bromo-3 : 5-dinitrobenzene of m. p. 77—78° (Found: Br, 32·0. Calc. for $C_6H_3O_4N_2Br$: Br, 32·3%). Elion (*Rec. Trav. chim.*, 1923, **42**, 145) gives m. p. 77°.

Pyridine was heated at 100° in a similar mixture for 2 days but gave no recognisable quantity of bromination product.

Bromination of Benzoic Acid with Bromine and Bromic Acid.—Benzoic acid (13 g., 0·1 mol.) and bromine (2·1 ml.) were dissolved in a mixture of glacial acetic acid (250 ml.) and concentrated sulphuric acid (150 ml.). A solution of potassium bromate (4 g. in 50 ml. of warm water) was added slowly during ½ hour, with vigorous stirring, and the temperature maintained at 25° by external cooling. Precipitation of *m*-bromobenzoic acid was noted after about 20 minutes' reaction. After the mixture had been stirred continuously for a further hour, a second, similar portion of potassium bromate solution was added slowly during ½ hour. Finally the precipitated *m*-bromobenzoic acid, m. p. 150—154° (11 g.), was collected on a sintered-glass filter, washed with a little water, and dried.

Brominations effected with Mercuric Nitrate.—(i) Benzene (15 ml.), bromine (5·2 ml.), acetic acid (400 ml.), and nitric acid [33 ml. (*d* 1·4) in 100 ml. of water] were stirred together at room temperature, and mercuric nitrate solution (17 g. in 75 ml. of water) was dropped in during ½ hour. The bromine had then disappeared. The product was diluted, partly neutralised (sodium carbonate), and repeatedly extracted with ether. The extract, when washed with alkali, dried, and fractionated, gave 10 g. (70%) of bromobenzene.

(ii) Benzoic acid (13 g., 0·1 mol.), bromine (5·2 ml.), glacial acetic acid, and nitric acid [55 ml. (*d* 1·4) and 50 ml. of water] were stirred together at about 23°, and an aqueous solution of mercuric nitrate (17 g. as above) was added during ½ hour; mercuric bromide was deposited. After a further ½ hour the solution was poured into water (2 l.), freed from bromine (sodium sulphite), and extracted with ether. The extract was freed from mercuric salts by means of hydrogen sulphide and then concentrated. From the residue 12 g. (60%) of pure *m*-bromobenzoic acid, m. p. and mixed m. p. 154—155°, were obtained by recrystallisation from alcohol–water.

The Stabilities of Some Aliphatic Compounds.—(i) *Acetic acid.* A product purified by fractional distillation from chromium trioxide, and stable both to free bromine and to potassium permanganate, was used. 20 Ml. were mixed with 20 ml. of 10*N*-sulphuric acid and 10 ml. of approx. 0·02*N*-hypobromous acid and kept in a thermostat at 17° for 20 minutes. There was no change in the potassium iodide–thiosulphate titre of the mixture.

(ii) *Propionic acid.* The acid was purified by heating 50 ml. with 2 g. of chromium trioxide on a steam-bath for 2 hours, and was finally fractionated under reduced pressure from fresh chromium trioxide. It had b. p. 55°/23 mm. and was stable to permanganate. A mixture of 5 ml. in 15 ml. of water, 20 ml. of 5*N*-sulphuric acid and 10 ml. of *ca.* 0·02*N*-hypobromous acid exhibited no titre change during 50 minutes' storage at room temperature.

(iii) *Methyl alcohol.* A sample, purified by refluxing with sodium hypoiodite, was distilled from silver nitrate and finally dried over quicklime and fractionated; it then had b. p. 66°/675 mm. A mixture similar to that of (ii) above showed no change in titre during 40 minutes.

(iv) *Dioxan.* 150 Ml. of dioxan, 8 ml. of bromine, and 60 ml. of 50% sulphuric acid were heated at 100° for ½ hour. Excess of bromine was removed with sulphur dioxide, and the solution was then made alkaline with aqueous potassium hydroxide. The lower aqueous layer was removed and the remaining dioxan was dried (KOH) and fractionated carefully. The pure product, b. p. 100·5°/767 mm., was stable both to cold neutral potassium permanganate solution and to an acid hypobromous acid solution similar to that used for (ii) above.

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109. *The Purification of Lutecium by Fractionation of Hexa-antipyrinelutecium Iodide.*

By JOSEPH K. MARSH.

It is demonstrated that fractionation of hexa-antipyrinelutecium iodide, $[Lu(C_{11}H_{12}N_2O)_4]I_3$, gives a very rapid purification. This is ascribed to a large complexing, rather than a solubility, differential. The separations of thulium and erbium, and of holmium and dysprosium, have also been noted.

THE favourable results obtainable by lanthanon tri(dimethyl phosphate) fractionation prompt a search for other compounds of a similar nature. Freed's suggestion (*J. Amer. Chem. Soc.*, 1931, **53**, 3906) that the use of non-solvated ions would permit of better fractionation than occurs with solvated ions would appear to be exemplified by the dimethyl phosphates. Few salts of the lanthanons, however, crystallise in the anhydrous state, and in these cases the metal ion appears to be complexed with some group other than water. Thus the six oxygen atoms attached to methyl groups of $Ln[PO_4Me_2]_3$ are probably complexed with the metal. The antipyrine addition compounds of the lanthanons are a noteworthy class of anhydrous salts (Kolb, *Z. anorg. Chem.*, 1913, **83**, 144; Riabtschikov and Terentieva, *Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **51**, 291), and from the solubility measurements of Wilke-Dörfurt and Schiliephake (*Z. anorg. Chem.*, 1928, **170**, 129) all the evidence points to a further resemblance to the dimethyl phosphates in that the lanthanum salts are the most soluble of the series. From published work the iodides seem most likely to constitute a favourable medium for fractionation. The solubility range is considerable, there being a 6·4-fold increase for lanthanum over the molar value for yttrium, the solubilities being 4·44 and 29·5 g./100 g. of water, respectively, at room temperature. A 26-fold increase occurs in the case of the dimethyl phosphates. The hexa-antipyrine lanthanon iodides form compact cubo-octahedral crystals, whereas the dimethyl phosphates give a fibrous pulp which generally requires filtration, thus much reducing the efficiency. Moreover, hydrolysis is too pronounced for erbium and elements of higher atomic number to be dealt with efficiently as dimethyl phosphates, whereas the antipyrine iodide compounds are stable.

By the aid of these compounds a crude lutecium product has shown a very rapid purification, and it seems probable that thulium and erbium may also be separated with reasonable efficiency. The separation of holmium and dysprosium has not proved so effective, though further work is required before it can be said definitely whether the method is useful or not, in this case.

The separation does not appear to be based upon solubility differences alone, for these are only moderate. It must depend rather upon the complexing strengths of the metals with antipyrine. The complex is much less soluble than its components, and normal lanthanon ions exist in its solution, indicating some dissociation, since oxalic acid gives the usual oxalate precipitate. The fractionation therefore is based on the crystallising out of the more strongly complexing elements. These are the more weakly basic and give slightly the less soluble complexes. Hexa-antipyrinelutecium iodide collects at the insoluble end of the series, thus providing a means of purification utilising the well-known principle that impurities are eliminated at the tail fraction preferably to the head. This is especially valuable, since lutecium is the end member of the series. The solubility of the iodide complex is such that only 10—20 g./l. of oxide are present in the fractionation series when hot, so that it is rather bulky. The solubility in methanol is considerably greater, and the same types of crystals are obtained. A mixed solvent might therefore prove useful, but a short fractionation in methanol indicated

that separation was much less pronounced in this solvent. The older methods of lutecium fractionation, by bromates or double ammonium oxalates, concentrate lutecium at the tail. The bromates are so soluble and the mother-liquors so viscous that the fractionation is difficult.

The initial fractional precipitation of some crude lutecium iodide by antipyrine gave a head fraction containing Tm_2O_3, 6·1; Er_2O_3, 0·7%, whereas the tail (fraction 9) contained 43% and 32%, respectively. Ten series of crystallisations produced a head with Tm_2O_3, 1·4%; Er_2O_3, nil; and a tail with 49% and 42%, respectively. Further work on a larger scale is in hand.

Experimental.

The lanthanons from a quantity of Norwegian gadolinite were fractionated by double sulphate precipitation till the oxide was free from any brown tint due to the presence of terbium. The terbium-free material was then fractionated by precipitation of basic salts till most of the yttrium had been removed but the thulium retained. The concentrate of weak bases was converted into acetate, and ytterbium removed by sodium amalgam. The residue was then fractionated as bromate, and tail fractions were taken off as soon as they became almost colourless; these consistituted the material used in this investigation.

10 G. of the crude lutecium oxide were dissolved in hydriodic acid (*d* 1·7) and excess of acid and iodine driven off on the water-bath. The salt was taken up in 400 ml. of hot water, and 20 ml. of antipyrine solution (400 g./l.) were added. A crop of hexa-antipyrinelutecium iodide was collected next day. Seven further crops were collected on subsequent days. The solution was concentrated to 100 ml. after the sixth crop, and a small residue (0·13 g. of oxide) was recovered from the final mother-liquor. After recrystallising twice, the first crop was converted into oxide (0·17 g.). The remaining crops were dissolved in boiling water, about 100 ml. being required for each. They crystallised on cooling and the mother-liquors were examined with a Beckman spectrophotometer (Model DU), thus affording an estimate of thulium and erbium present. The series was then fractionated systematically ten times in 8—10 fractions, the tail fractions being allowed to become small. Head and tail fractions were then again recovered as oxide (1·0 and 0·2 g.). The series of mother-liquors were again examined spectrophotometrically. The two sets of heads and tails were made up as chloride solutions (33·3 g./l. of oxide, except the head fraction after fractional crystallisation, which was 150 g./l.). All were examined in 1-cm. cells using the bands λλ 940, 684, and 524 mμ. for Yb, Tm, and Er estimations, respectively, checked against standard chloride solutions. In the case of the mother-liquors the assumption was made that a calibration with chloride solutions was admissible for estimating the antipyrine complex in solution. Some yellow colour had developed in fractions 13 and 14 so that here erbium estimates are probably high. The results are set out below.

Initial split.

Fraction:	3.	4.	5.	6.	7.	8.	1.	9.
Tm_2O_3	0·81	1·06	1·55	3·16	4·46	5·20 g./l.	6·1%	54%
Er_2O_3	0·20	0·40	0·60	1·22	2·31	3·80 g./l.	0·7%	32%

After ten series of crystallisations.

Fraction:	6.	7.	8.	9.	10.	11.	12.	13.	14.	5.	15.
Tm_2O_3	0·24	0·73	1·55	2·2	3·0	3·3	3·9	3·0	3·0 g./l.	1·4%	49%
Er_2O_3 ...	0·00	0·00	0·07	0·41	0·41	0·75	1·8	3·5	5·4 g./l.	nil	42%
Volume	90	90	90	70	70	70	60	30	20 ml.	2·4% of Yb_2O_3	

Holmium and Dysprosium.—A mixture of holmium and dysprosium oxides (3·5 g.) was given a similar treatment to that described above for the initial split into hexa-antipyrinelutecium iodide fractions. The first crop and final mother-liquor were recovered as oxides (0·1 g. each). The oxide of the head fraction was a deep cream, but the tail a bright brown, indicating a good concentration of terbium oxide in the tail fraction. Chloride solutions were prepared (33·3 g./l. of oxide) and examined spectrophotometrically with the following results: Ho_2O_3, Head 15·1%, Tail 7·2%. Dy_2O_3, Head 52·5%, Tail 54%.

Solubilities.—3·190 G. of mother-liquor from fraction 6 of the hexa-antipyrinelutecium iodide, after standing for 2 days at room temperature after the series of ten fractionations, were evaporated to constant weight on the water-bath and yielded 0·124 g. of solid = 4·05 g./100 g. of water; Lu_2O_3 = 4·82 g./l. A similar determination on the head fraction of the dysprosium material gave 6·15 g./100 g. of water; Dy_2O_3 = 6·86 g./l.

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110. *Dithiols. Part IV. The Reaction of Toluene-p-sulphonates and Methanesulphonates with Potassium Thiolacetate : A New Method for the Preparation of Thiols.*

By J. H. Chapman and L. N. Owen.

The reaction of primary toluene-*p*-sulphonates, ROTs, with potassium thiolacetate, in ethanol or acetone, provides a useful method for the preparation of thiolacetates, RSAc, and thence, by hydrolysis, of thiols.

Secondary toluene-*p*-sulphonates show wide differences in behaviour. The simple compounds, *e.g.*, the *iso*propyl ester, and certain vicinal ditoluene-*p*-sulphonates where the adjacent group is primary, *e.g.*, the ditoluene-*p*-sulphonyl derivative of propane-1 : 2-diol, react normally, though the replacement of the secondary group requires conditions more vigorous than those necessary for reaction of the primary group. In more complex substances, *e.g.*, the 3-toluene-*p*-sulphonate of 1 : 2-5 : 6-di*iso*propylidene glucose, the reaction does not occur. *cyclo*Hexyl toluene-*p*-sulphonate gives mainly *cyclo*hexene; phenyl toluene-*p*-sulphonate is non-reactive.

Several methanesulphonates have been examined and, with one exception, their reactions follow the same course as with the corresponding toluene-*p*-sulphonates, but the yields are inferior.

The difference in reactivity between primary and secondary toluene-*p*-sulphonates in the exchange reaction has been used to establish the structure of the *2-toluene*-p-*sulphonate* 1-*benzoate* of propane-1 : 2-diol (*2-toluene*-p-*sulphonyloxypropyl* 1-*benzoate*.)

In connection with the preparation of dithiols with potential antiarsenical pharmacological properties (cf. Part III; Evans, Fraser, and Owen, *J.*, 1949, **248**) it occurred to us that the well-known reactivity of toluene-*p*-sulphonates might be applied to the formation of thiolacetates by carrying out an exchange reaction with potassium thiolacetate :

$$ROTs + AcSK \longrightarrow RSAc + TsOK \quad (Ts = \text{toluene-}p\text{-sulphonyl})$$

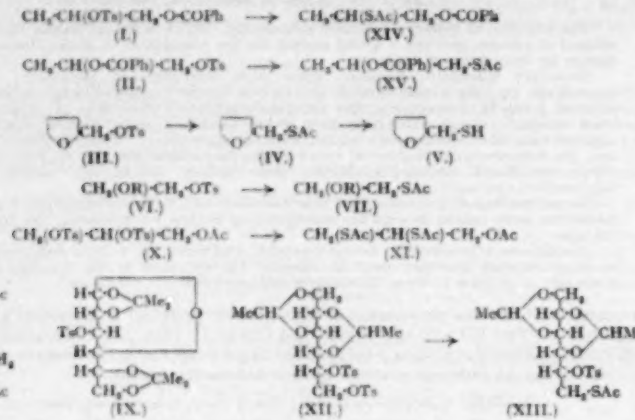
Some encouragement for this supposition was afforded by the earlier observations of Gilman and Beaber (*J. Amer. Chem. Soc.*, 1925, **47**, 1449) and of Raymond (*J. Biol. Chem.*, 1934, **107**, 85), who had shown that toluene-*p*-sulphonates react with the alkali-metal derivatives of aliphatic and aromatic thiols to give sulphides. Furthermore, the preparation of carbohydrate thiocyanates, by reaction of the toluene-*p*-sulphonates with potassium thiocyanate, had been recorded by Müller and Wilhelms (*Ber.*, 1941, **74**, 698) and by Carson and Maclay (*J. Amer. Chem. Soc.*, 1948, **70**, 2220).

Such a reaction, if successful, would provide a useful method for the conversion of a hydroxyl group into a thiol group by the sequence ROH $\longrightarrow$ ROTs $\longrightarrow$ RSAc $\longrightarrow$ RSH, and might be of particular value for the preparation of certain polyhydroxy-thiols where the corresponding halogen derivatives (necessary for the older method involving R·Hal $\longrightarrow$ RSAc) are not easily accessible. In the carbohydrate field, for example, relatively few halogen derivatives are known, whereas a large number of toluene-*p*-sulphonates are readily available.

Since the reactivity of sulphonyl esters is markedly affected by the nature of the esterifying group, particularly by its primary or secondary character (cf. Clarke and Owen, *J.*, 1949, 315; Owen and Robins, *ibid.*, pp. 320, 326; and references there cited), it was necessary to study the reaction with potassium thiolacetate by the use of several types of compounds. The majority of these were toluene-*p*-sulphonates, but in view of the increasing interest in methanesulphonyl derivatives some of the latter were also investigated. Many of the starting materials were previously known compounds, and were prepared by standard methods; some, however, were new or exhibited some points of interest. *2-Methoxyethyl methanesulphonate*, *propylene* 1 : 2-*dimethanesulphonate*, and *propylene* 1 : 2-*ditoluene*-p-*sulphonate* were prepared by treatment of the corresponding hydroxy-compounds with the appropriate sulphonyl chloride in pyridine. *3-Acetoxypropylene* 1 : 2-*ditoluene*-p-*sulphonate* was obtained by reaction of 2 : 3-dibromopropyl acetate with silver toluene-*p*-sulphonate. In an attempt to prepare a monotoluene-*p*-sulphonate of propane-1 : 2-diol, propylene oxide was treated with toluene-*p*-sulphonic acid in dry ether; an oily product was obtained, which by benzoylation gave a solid, separable by fractional crystallisation into two substances, m. p.s 105° and *ca.* 79°. The latter was eventually shown, by reaction with potassium thiolacetate, to be a mixture of the isomeric compounds (I) (identical with the substance of m. p. 105°) and (II), which could not readily be separated by further fractional crystallisation.

Preliminary experiments showed that the toluene-*p*-sulphonyloxy- and the methanesulphonyloxy-residues, particularly when primary, were readily replaceable by the acetylthio-

group. Benzyl toluene-*p*-sulphonate showed exceptional reactivity; when it was dissolved in cold alcoholic potassium thiolacetate a precipitate of potassium toluene-*p*-sulphonate began to form almost immediately, and the reaction was complete within 15 minutes at room temperature. In general, however, the replacement was carried out by heating the reaction mixture in ethanol or acetone under reflux, using about twice the theoretical quantity of



potassium thiolacetate; in many cases this excess is unnecessary for general preparative purposes, but was used in the present experiments in order that the yields of thiolacetates could be determined, under comparable conditions, for all the substances used. Potassium thiolacetate is readily soluble in ethanol, and the solid precipitated during the reactions in this solvent was almost pure potassium toluene-*p*-sulphonate. The reagent, however, is only sparingly soluble in acetone, and, since it was found to be unnecessary to use the large amount of solvent which would have been required to give complete solution, the solid remaining after completion of the reactions in acetone was a mixture of potassium toluene-*p*-sulphonate and unchanged potassium thiolacetate. All the primary compounds, and some secondary, gave the corresponding thiolacetates under these conditions, usually in good yield. With the primary compounds the reaction mixture became only slightly discoloured during the heating, but a deep red colour developed when secondary compounds were used. Hydrolysis of the thiolacetates afforded the free thiols.

Tetrahydrofurfuryl toluene-*p*-sulphonate (III), in contrast to benzyl toluene-*p*-sulphonate, reacted only slowly at room temperature, but in the boiling solvent (acetone or ethanol) it gave a good yield of tetrahydrofurfuryl thiolacetate (IV). Alkaline hydrolysis of the latter readily gave 2-*mercaptomethyltetrahydrofuran* (*tetrahydrofurylmethanethiol*) (V), though acid hydrolysis furnished only a small yield of the thiol, probably owing to simultaneous ring-fission. Tetrahydrofurfuryl methanesulphonate reacted much less readily than the toluene-*p*-sulphonate, and a longer period of heating was necessary. This observation is of interest in that a reverse order of reactivity is shown by these sulphonates in their reactions with potassium cyanide (Zief, Fletcher, and Kirshen, *J. Amer. Chem. Soc.*, **1946**, **68**, 2743); furthermore, earlier investigators have usually reported a greater reactivity for the methansulphonates in reactions with, *e.g.*, sodium iodide (*inter al.*, Helferich and Gnüchtel, *Ber.*, **1938**, **71**, 712).

n-Propyl toluene-*p*-sulphonate gave a better yield of *n*-propyl thiolacetate when acetone, rather than ethanol, was used, and it is probable that with the simple sulphonates of low molecular weight the competitive etherification reaction ROTs + EtOH ⟶ ROEt, when ethanol is used as a solvent, results in a diminished yield of thiolacetate; this was particularly apparent in the reaction with *iso*propyl toluene-*p*-sulphonate (see below).

Trimethylene ditoluene-*p*-sulphonate gave an excellent yield of the bisthiolacetate, and thence, by hydrolysis, 1 : 3-dimercaptopropane was obtained.

The possible effect of a neighbouring ether group was investigated by reactions using

2-methoxyethyl toluene-*p*-sulphonate (VI; R = Me) and methanesulphonate; *2-methoxyethyl thiolacetate* (VII; R = Me) was obtained in each case, but again the methanesulphonate was the less reactive. Hydrolysis of the product gave *2-methoxyethanethiol*. Similarly, 2-phenoxyethyl toluene-*p*-sulphonate (VI; R = Ph) gave an almost quantitative yield of *2-phenoxyethyl thiolacetate* (VII; R = Ph), and thence a high yield of *2-phenoxyethanethiol*. 2-Benzoyloxyethyl toluene-*p*-sulphonate (VI; R = COPh) afforded an example of a substance with a neighbouring ester group; it gave *2-benzoyloxyethyl thiolacetate* (VII; R = COPh), hydrolysed to 2-hydroxyethanethiol (2-mercaptoethanol). 1 : 6-Ditoluene-*p*-sulphonyl 2 : 3-4 : 5-dimethylene mannitol yielded 1 : 6-diacetyl 2 : 3-4 : 5-dimethylene 1 : 6-dithiomannitol [VIII; position of methylene residues not finally established (compare Haworth and Wiggins, *J.*, 1944, 61)].

Of the secondary toluene-*p*-sulphonates, the *iso*propyl ester reacted readily in boiling ethanol but, although potassium toluene-*p*-sulphonate was formed to the extent of 80% of the theoretical in 30 minutes, the yield of propane-2-thiol was only 6%; no propylene could be detected, and the main product was probably ethyl *iso*propyl ether, since a much better yield of thiolacetate was obtained in acetone solution. With *cyclo*hexyl toluene-*p*-sulphonate, on the contrary, poor yields of *cyclo*hexyl thiolacetate were obtained both in ethanol and in acetone, *cyclo*hexene being formed in each case; this elimination reaction is not unexpected, in view of similar results which have been observed when secondary alicyclic toluene-*p*-sulphonates are treated with a variety of reagents (Hückel, Neunhoeffer, Gercke, and Frank, *Annalen*, 1930, **477**, 143; Clarke and Owen, *loc. cit.*; Owen and Robins, *loc. cit.*). 3-Toluene-*p*-sulphonyl 1 : 2-5 : 6-di*iso*propylidene glucose (IX) failed to react with potassium thiolacetate in acetone at 110°.

The ditoluene-*p*-sulphonates of propane-1 : 2-diol and of 2 : 3-dihydroxypropyl acetate (X) provided examples of compounds containing vicinal primary and secondary sulphonyloxy-groups. In acetone solution, the primary and the secondary groups in both compounds were replaced, to give moderate yields of 1 : 2-bisacetylthiopropane and 2 : 3-bisacetylthiopropyl acetate ("BAL" triacetate) (XI), respectively. The dimethanesulphonate of propane-1 : 2-diol was somewhat less reactive than the corresponding ditoluene-*p*-sulphonate, but gave the same product as the latter. In striking contrast was the behaviour of the 5 : 6-ditoluene-*p*-sulphonate of 1 : 3-2 : 4-diethylidene sorbitol (XII) in which, even after vigorous treatment, only the primary group could be replaced, to give *6-acetyl 5-toluene-*p*-sulphonyl* 1 : 3-2 : 4-*diethylidene 6-thiosorbitol* (XIII). The corresponding 5 : 6-dimethanesulphonate appeared to undergo some reaction, but gave no recognisable product.

The only aryl compound studied, phenyl toluene-*p*-sulphonate, failed to react with potassium thiolacetate.

The results are summarised in the table, in which the yields refer to distilled or crystalline thiolacetates. It is clear from these experiments that the reaction of primary toluene-*p*-sulphonates with potassium thiolacetate provides a good method for the preparation of primary thiolacetates, and thence of the corresponding thiols, but that the behaviour of a secondary toluene-*p*-sulphonyloxy-group is capable of wide variation, ranging from non-reactivity to comparatively smooth replacement, with the possibility also of the occurrence of an elimination reaction and formation of an unsaturated product. The course taken in any particular case depends on the molecular environment, and the structural factors concerned merit further study, particularly since comparable variations are already known to occur in the reactions of secondary toluene-*p*-sulphonates with other reagents, *e.g.*, potassium acetate, sodium iodide. An interesting example of a carbohydrate derivative possessing two reactive secondary methanesulphonyl groups is discussed in Part V (following paper).

These experiments demonstrated a marked difference in reactivity between primary and secondary sulphonyloxy-groups, and thus provided a novel means of investigating the structures of the toluene-*p*-sulphonate–benzoates of propane-1 : 2-diol, m. p.s 105° and 79°, to which reference was made above. When the lower-melting material was boiled with potassium thiolacetate in acetone for an hour, a mixture was obtained, consisting of a liquid thiolacetate–benzoate, together with the crystalline toluene-*p*-sulphonate–benzoate, m. p. 105°. The latter was recovered almost quantitatively after further treatment under the same conditions, but under more vigorous conditions it reacted slowly to give a different thiolacetate–benzoate. It follows from these differences in reactivity that the compound of m. p. 105° contains a secondary toluene-*p*-sulphonyl group, and must therefore be the *2-toluene-*p*-sulphonate 1-benzoate* (I); the material of m. p. 79° is evidently a mixture of (I) with the isomeric 1-toluene-*p*-sulphonate 2-benzoate (II). During the short period of reaction the latter is converted into the *2-benzoate*

1-*thiolacetate* (XV), whilst (I) is unaffected; more drastic treatment subsequently converts (I) into the 1-*benzoate* 2-*thiolacetate* (XIV). Independent confirmation of the structure of (I) has been provided by Mr. G. A. Haggis (unpublished work), who has shown that on reaction with sodium iodide, followed by hydrogenation, it gives *n*-propyl benzoate.

The reaction of sulphonic esters with potassium thiolacetate.

(Ts = toluene-*p*-sulphonate; Ms = methanesulphonate.)

Ester.	Solvent.	Time at b. p., hrs.	Yield of thiolacetate, %.
Benzyl Ts	EtOH	1	79
Tetrahydrofurfuryl Ts	EtOH	1	71
	Me_2CO	1	69
Tetrahydrofurfuryl Ms	Me_2CO	1	20
	Me_2CO	6	60
n-Propyl Ts	EtOH	0·5	55
	Me_2CO	0·5	72
Propane-1 : 3-diol di-Ts	EtOH	1	88
2-Methoxyethyl Ts	EtOH	1	67
	Me_2CO	1	69
2-Methoxyethyl Ms	Me_2CO	1	56
2-Phenoxyethyl Ts	EtOH	1	92
2-Benzoyloxyethyl Ts	EtOH	1	70
2 : 3 : 4 : 5-Dimethylene mannitol 1 : 6-di-Ts	Me_2CO	6	89
*iso*Propyl Ts	EtOH	0·5	6
	Me_2CO	2	49
	Me_2CO	6	71
*cyclo*Hexyl Ts	EtOH	0·25	19
1 : 2-5 : 6-Diisopropylidene glucose 3-Ts	Me_2CO	18 *	0
Propane-1 : 2-diol di-Ts	Me_2CO	6	50
	Me_2CO	8	60
	Me_2CO	12	58
Propane-1 : 2-diol di-Ms	Me_2CO	4	38
	Me_2CO	6	43
Propane-1 : 2-diol 1-benzoate 2-Ts	Me_2CO	15 *	56
2 : 3-Dihydroxypropyl acetate di-Ts	Me_2CO	8	68
1 : 3-2 : 4-Diethylidene sorbitol 5 : 6-di-Ts	Me_2CO	6	87 †
1 : 3-2 : 4-Diethylidene sorbitol 5 : 6-di-Ms	Me_2CO	6	0
1 : 3-2 : 4-Diethylidene sorbitol 6-thiolacetate 5-Ts	Me_2CO	15 *	0
Phenyl Ts	Me_2CO	18 *	0

* Reaction at 110°. † Primary group only.

Experimental.

(M. p.s were determined on the Koefler block, and are corrected.)

Preparation of the Sulphonic Esters.—The following were made by published methods: benzyl toluene-*p*-sulphonate, m. p. 58° (Tipson, *J. Org. Chem.*, 1944, **9**, 235); tetrahydrofurfuryl toluene-*p*-sulphonate, m. p. 37—38°, after distillation at 110° (bath) 0·0001 mm. (Barger, Robinson, and Urushibara, *J.*, 1937, 714; also obtained by the general method of Tipson, *loc. cit.*); tetrahydrofurfuryl methanesulphonate, b. p. 116°/1 mm., n_D^{25} 1·4613 (Zief, Fletcher, and Kirshen, *loc. cit.*); 2-methoxyethyl toluene-*p*-sulphonate, b. p. 120—130°/0·1 mm. (Tipson, *loc. cit.*); 2-phenoxyethyl toluene-*p*-sulphonate, m. p. 81° (Tipson, *loc. cit.*); 2 : 3 : 4 : 5-dimethylene mannitol 1 : 6-ditoluene-*p*-sulphonate, m. p. 164° (Haworth and Wiggins, *J.*, 1944, 61); *cyclo*hexyl toluene-*p*-sulphonate, m. p. 43° (Hückel, Neunhoeffer, Gercke, and Frank, *loc. cit.*); 1 : 2-5 : 6-diisopropylidene glucose 3-toluene-*p*-sulphonate, m. p. 120° (Freudenberg and Ivers, *Ber.*, 1922, **55**, 929); phenyl toluene-*p*-sulphonate, m. p. 95° (Reverdin and Crépieux, *Ber.*, 1902, **35**, 1443).

n-Propyl toluene-*p*-sulphonate was prepared by treatment of *n*-propanol (30 g.) in pyridine (250 c.c.) with toluene-*p*-sulphonyl chloride (105 g.) at −5° until all the chloride had dissolved, followed by 4 hours at 0°. The solution was then poured into ice-cold 5*N*-sulphuric acid (750 c.c.), and the oil was taken up in chloroform; the extract was washed with 2*N*-sulphuric acid and with sodium hydrogen carbonate solution, dried (K_2CO_3), and evaporated to an oil. The product (88 g., 82%) distilled at b. p. 134°/0·4 mm., n_D^{25} 1·5069.

The propylene 1 : 3-ditoluene-*p*-sulphonate was obtained from the diol (8 g.), toluene-*p*-sulphonyl chloride (44 g.), and pyridine (175 c.c.). After 1 hour at 0°, addition of 5*N*-sulphuric acid precipitated the ester as a solid, which formed plates, m. p. 92°, from methanol; yield, 27 g. (70%) (Found: C, 53·4; H, 5·2. Calc. for $C_{17}H_{20}O_6S_2$: C, 53·1; H, 5·25%) (cf. King, *J.*, 1928, 2426).

2-Benzoyloxyethyl toluene-*p*-sulphonate was prepared from 2-benzoyloxyethanol (Cretcher and Pittenger, *J. Amer. Chem. Soc.*, 1925, **47**, 2560) by a modification of the method of Butler *et al.* (*ibid.*, 1935, **57**, 575). The alcohol (20 g.), toluene-*p*-sulphonyl chloride (11·5 g.), and pyridine (100 c.c.), after being mixed at 0°, were kept at room temperature for 4 hours, and gave 23·6 g. (61%) of the ester (Butler *et al.*, *loc. cit.*, using less pyridine, recorded a yield of 26%).

Treatment of 2-methoxyethanol (10 g.) in pyridine (100 c.c.) with methanesulphonyl chloride

(16·6 g.), below −5° and then 12 hours at *ca.* 15°, dilution with water, and extraction of the product with chloroform, gave *2-methoxyethyl methanesulphonate* (14·6 g., 72%), b. p. 80°/0·4 mm., n_D^{20} 1·4314 (Found: C, 31·1; H, 6·5. $C_4H_{10}O_4S$ requires C, 31·15; H, 6·55%).

*iso*Propyl toluene-*p*-sulphonate, n_D^{20} 1·5040, was prepared in the same way as the *n*-propyl ester.

Treatment of propane-1 : 2-diol (5 g.) in pyridine (150 c.c.) with toluene-*p*-sulphonyl chloride (28 g.) at 0° for 1 hour and at room temperature overnight gave, on pouring of the mixture into dilute sulphuric acid, a precipitate of the *ditoluene-p-sulphonate*, which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 68—69° (Found: C, 53·0; H, 4·95. $C_{17}H_{20}O_6S_2$ requires C, 53·1; H, 5·25%). The *dimethanesulphonate*, prepared in a similar way, crystallised from the same solvent in rectangular tablets, m. p. 53° (Found: C, 25·85; H, 5·25. $C_5H_{12}O_6S_2$ requires C, 25·85; H, 5·2%).

2 : 3-*Ditoluene-p-sulphonyloxypropyl acetate* was obtained by heating under reflux a solution of 2 : 3-dibromopropyl acetate (10 g., b. p. 130°/32 mm.; n_D^{20} 1·5060) in benzene (100 c.c.) with silver toluene-*p*-sulphonate (25 g.) for 15 hours. The filtered solution was then washed with aqueous sodium hydrogen carbonate, and evaporated to an oil, which crystallised on addition of light petroleum and formed needles (5·45 g., 32%), m. p. 100°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 51·5; H, 5·1. $C_{19}H_{20}O_8S_2$ requires C, 51·55; H, 5·0%).

The dimethane sulphonate of 1 : 3-2 : 4-diethylidene sorbitol was obtained by the method described in Part VII. The corresponding ditoluene-*p*-sulphonate was prepared by addition of toluene-*p*-sulphonyl chloride (8·95 g.) to a solution of 1 : 3-2 : 4-diethylidene sorbitol (5 g.) in pyridine (20 c.c.) at 0°. After 12 hours at *ca.* 5°, addition of water gave the solid derivative (7·9 g.), m. p. 173°, $[\alpha]_D^{20}$ −11·3° (*c*, 1 in chloroform), after recrystallisation from methanol (cf. Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837; Wiggins, *J.*, 1946, 388).

Reaction of Propylene Oxide with Toluene-p-sulphonic Acid.—To a solution of the oxide (9 g.) in dry ether (150 c.c.), dry toluene-*p*-sulphonic acid (27 g., 1 mol.) was added in small portions, and the solution was then kept overnight. During this time a lower oily layer was formed. The solvent was removed under reduced pressure, and the residual oil was dissolved in chloroform, washed with water and with sodium hydrogen carbonate solution, and dried. Evaporation of the solvent then gave a pale yellow viscous oil (33 g.). This was dissolved in pyridine (150 c.c.) and treated with benzoyl chloride (25 g.), with cooling. After 1 hour at 15°, water was added, and the precipitated oil was taken up in chloroform and washed with dilute sulphuric acid, sodium hydrogen carbonate, and finally with water. The dried solution was then evaporated, and gave a semi-solid residue. One recrystallisation from benzene–light petroleum (b. p. 60—80°) gave 35 g. of material, m. p. *ca.* 70—75°, from which, by several recrystallisations from methanol, *2-toluene-p-sulphonyloxypropyl 1-benzoate* was obtained; it formed needles or plates, m. p. 105° (Found: C, 61·4; H, 5·7. $C_{17}H_{18}O_5S$ requires C, 61·05; H, 5·4%). The main portion of the reaction product, recovered from the mother-liquors, was a mixture of the structural isomers; after repeated crystallisations from benzene–light petroleum or from methanol it gave colourless needles, m. p. *ca.* 79° (Found: C, 60·8; H, 5·6%).

Reaction of Sulphonic Esters with Potassium Thiolacetate.—The conditions for each experiment are given individually below, and the yields of thiolacetates are summarised in the table. Except where otherwise stated, reaction products were worked up by the following procedure. The cooled mixture was filtered, and the salts were washed with cold solvent. The ethanol or acetone filtrate and washings were concentrated to small bulk and then diluted with water. The product, if solid, was collected, washed, and recrystallised; if liquid, it was extracted with ether, the extracts were washed with water, then dried and evaporated, and the residual oil was purified by distillation.

Hydrolysis of Thiolacetates to Thiols.—(a) *Alkaline hydrolysis.* The thiolacetate was dissolved in cold 5% methanolic potassium hydroxide (2·1 mols. of KOH per acetylthio-group) and left overnight, under nitrogen, at room temperature. A slight excess of hydrochloric acid was then added, with cooling, and after removal of methanol under reduced pressure the thiol was isolated by ether-extraction.

(b) *Acid hydrolysis.* The thiolacetate was dissolved in ten times its weight of N-methanolic hydrogen chloride and boiled under reflux for 4 hours under nitrogen. The cooled solution was then diluted with water, concentrated under reduced pressure to remove methanol, and extracted with ether to obtain the thiol.

The yields of thiol, recorded below in the individual cases, are based on thiolacetates, and are not overall yields.

Quantitative Determination of Thiol Values.—The method described in Part II (Evans and Owen, *J.*, 1949, 244) was used, except that with non-water-soluble thiols sufficient methanol was added to effect dissolution in the hydrochloric acid before titration with iodine.

Benzyl Thiolacetate.—(*a*) Benzyl toluene-*p*-sulphonate (1 g.) and potassium thiolacetate (1 g.) were separately dissolved in the minimum amount of ethanol. On mixing of the cold solutions, a copious white precipitate was formed within a few minutes. After 10 minutes, the potassium toluene-*p*-sulphonate (0·6 g., 75%) was filtered off and washed with cold ethanol.

(*b*) The toluene-*p*-sulphonate (5 g.) and potassium thiolacetate (5 g.) were heated in ethanol (250 c.c.) under reflux, and gave benzyl thiolacetate (2·5 g.), b. p. 54°/0·05 mm., n_D^{20} 1·5578, which on acid hydrolysis furnished toluene-α-thiol, b. p. 100°/22 mm. (Found: thiol S, 25·4. Calc. for C_7H_8S: S, 25·8%).

Tetrahydrofurfuryl Thiolacetate.—The toluene-*p*-sulphonate reacted only slowly with potassium thiolacetate in ethanol at room temperature, replacement being incomplete after 10 days. The toluene-*p*-sulphonate (14 g.) or the methanesulphonate (6 g.), with potassium thiolacetate (12·5 g. or 7·5 g. respectively), on being heated under reflux, in acetone or ethanol (100 c.c.), gave the *thiolacetate*, b. p. 107°/16 mm., n_D^{20} 1·4941 (Found: C, 52·4; H, 7·65. $C_7H_{12}OS$ requires C, 52·5; H, 7·55%). Light absorption: max. 2300 A., ε 4800. Alkaline hydrolysis then gave *2-mercaptomethyltetrahydrofuran* (55%), b. p. 113°/145 mm., n_D^{20} 1·4910 (Found: C, 50·5; H, 8·8; thiol S, 26·7. $C_5H_{10}OS$ requires C, 50·8; H, 9·1; S, 27·1%). The *phenylurethane*, prepared by treatment of the thiol with a slight excess of phenyl *iso*cyanate for 4 days at room temperature, crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 99° (Found: N, 6·1. $C_{12}H_{15}O_2NS$ requires N, 5·9%).

n-*Propyl Thiolacetate*.—The toluene-*p*-sulphonate (10 g.), potassium thiolacetate (11 g.), and acetone (100 c.c.) were heated under reflux, and gave the thiolacetate (4 g.), b. p. 141°, n_D^{20} 1·4590 (Wallach and Bleibtreu, *Ber.*, 1879, **12**, 1062, give b. p. 135—137°).

1 : 3-*Bisacetylthiopropane*.—The ditoluene-*p*-sulphonate of propane-1 : 3-diol (9 g.) and potassium thiolacetate (10·5 g.) were heated under reflux in ethanol (200 c.c.), and gave the bisthiolacetate (4 g.), b. p. 152°/24 mm., n_D^{20} 1·5200, which on acid hydrolysis furnished propane-1 : 3-dithiol (57%), b. p. 110°/120 mm., n_D^{20} 1·5390 (Found: thiol S, 59·1. Calc. for $C_3H_8S_2$: S, 59·3%).

2-*Methoxyethyl Thiolacetate*.—The toluene-*p*-sulphonate (10 g.) or the methanesulphonate (9·4 g.) was treated with potassium thiolacetate (10 g. or 13·5 g., respectively) in the boiling solvent (100 c.c.). The *thiolacetate* had b. p. 110°/110 mm., n_D^{20} 1·4645 (Found: C, 44·7; H, 7·45. $C_5H_{10}O_2S$ requires C, 44·8; H, 7·55%). Light absorption: max. 2280 A., ε 2600.

Hydrolysis of the thiolacetate (8 g.) under acid conditions gave, on evaporation of the solvent, no thiol; owing to its volatility in methanol it was present in the distillate, which was therefore made alkaline by the addition of 10% methanolic potassium hydroxide (70 c.c.) and evaporated to dryness under nitrogen. The residue was acidified with concentrated hydrochloric acid and extracted with ether. The dried extract was evaporated, the ether being removed through a 10" Vigreux column, and the residue on distillation gave 2-*methoxyethanethiol* (3 g., 55%), b. p. 112°, n_D^{20} 1·4488 (Found: C, 39·75; H, 9·0; thiol S, 34·1. C_3H_8OS requires C, 39·1; H, 8·75; S, 34·8%).

Treatment of the thiol (42 mg.) with 1-chloro-2 : 4-dinitrobenzene (100 mg.) and 2% aqueous sodium hydroxide (1·0 c.c.) in boiling ethanol (10 c.c.) for 10 minutes, followed by addition of water, gave 2 : 4-*dinitrophenyl* 2-*methoxyethyl sulphide* (95 mg.), which crystallised from ethanol in bright yellow plates, m. p. 90° (Found: N, 10·95. $C_9H_{10}O_5N_2S$ requires N, 10·85%).

2-*Phenoxyethyl Thiolacetate*.—The toluene-*p*-sulphonate (10 g.) and potassium thiolacetate (8 g.) in boiling ethanol (150 c.c.) gave the *thiolacetate*, which crystallised from methanol in plates, m. p. 48° (Found: C, 61·4; H, 6·4. $C_{10}H_{12}O_2S$ requires C, 61·4; H, 6·2%). On acid hydrolysis it gave 2-phenoxyethanethiol (90%), b. p. 134°/29 mm., n_D^{20} 1·5597 (Found: C, 62·3; H, 6·4; thiol S, 20·6. $C_8H_{10}OS$ requires C, 62·3; H, 6·5; S, 20·8%); the *phenylurethane* of this thiol formed needles, m. p. 113°, from light petroleum (b. p. 60—80°) (Found: N, 5·3. $C_{15}H_{15}O_2NS$ requires N, 5·15%).

2-*Benzoyloxyethyl Thiolacetate*.—The toluene-*p*-sulphonate (10 g.) and potassium thiolacetate (7 g.) were heated under reflux in ethanol (150 c.c.). The thiolacetate (4·7 g.) had b. p. 117°/0·1 mm., n_D^{20} 1·5446 (Found: C, 58·5; H, 5·4. $C_{11}H_{12}O_3S$ requires C, 58·9; H, 5·4%). On acid hydrolysis, 2-hydroxyethanethiol (52%), b. p. 65°/17 mm., was obtained, and was characterised as the bisphenylurethane, m. p. and mixed m. p. with an authentic sample, 146°.

1 : 6-*Diacetyl* 2 : 3-4 : 5-*Dimethylene* 1 : 6-*Dithiomannitol*.—The ditoluene-*p*-sulphonate (1 g.) was treated with potassium thiolacetate (0·9 g.) in boiling acetone (25 c.c.). The solid product, recrystallised from aqueous ethanol, furnished colourless needles of the *bisthiolacetate*, m. p. 109°, $[\alpha]_D^{20}$ +167° (*c*, 1·2 in chloroform) (Found: C, 44·8; H, 5·6; S, 19·8. $C_{12}H_{18}O_4S_2$ requires C, 44·7; H, 5·6; S, 19·9%). Light absorption: max. 2290 A., ε 11,000.

*iso*Propyl *Thiolacetate*.—The toluene-*p*-sulphonate (10 g.), in boiling ethanol or acetone (100 c.c.), was treated with potassium thiolacetate (11 g.), and gave *iso*propyl thiolacetate, b. p. 123°, n_D^{20} 1·4528 (Wallach and Bleibtreu, *loc. cit.*, give b. p. 124—127°).

cyclo*Hexyl Thiolacetate*.—When *cyclo*hexyl toluene-*p*-sulphonate (10 g.) and potassium thiolacetate (9 g.) were heated under reflux in ethanol (50 c.c.), a rapid reaction occurred and the mixture became deep red; after being heated for 15 minutes, it was worked up and gave 8·15 g. (98%) of potassium toluene-*p*-sulphonate. The solvent was removed through a 12" Vigreux column, and the first runnings contained much *cyclo*hexene, identified by its characteristic odour and unsaturation towards bromine. The small residue, on distillation, gave *cyclo*hexyl thiolacetate (1·2 g.), b. p. 130°/110 mm., n_D^{20} 1·5091 (Cunneen, *J.*, 1947, 134, gives b. p. 90°/14 mm.).

1 : 2-*Bisacetylthiopropane*.—The ditoluene-*p*-sulphonate or dimethanesulphonate of propane-1 : 2-diol (10 g.) was heated with potassium thiolacetate (6 g. or 10 g., respectively) in acetone (100 c.c.), and gave the bisthiolacetate, b. p. 93°/1 mm., n_D^{20} 1·5197 (Found: C, 43·45; H, 6·25. $C_7H_{12}O_2S_2$ requires C, 43·7; H, 6·3%).

2 : 3-*Bisacetylthiopropyl Acetate*.—The toluene-*p*-sulphonate (5 g.) and potassium thiolacetate (6·5 g.) were heated under reflux in acetone (100 c.c.), and gave the triacetate of 2 : 3-dimercaptopropanol (1·9 g.), b. p. 120°/0·05 mm., n_D^{20} 1·5105 (Evans and Owen, *loc. cit.*, found n_D^{20} 1·5140); on acid hydrolysis, 2 : 3-dimercaptopropanol was obtained, b. p. 81°/1 mm., n_D^{20} 1·5710 (Found: thiol S, 49·8. Calc. for $C_3H_8OS_2$: S, 51·6%).

Non-interaction of Potassium Thiolacetate and 3-*Toluene-p-sulphonyl* 1 : 2-5 : 6-*Diisopropylidene Glucose*.—The toluene-*p*-sulphonate (1 g.), potassium thiolacetate (0·55 g.), and acetone (50 c.c.) were heated at 110° in a sealed tube for 18 hours. Unchanged toluene-*p*-sulphonate (0·9 g.) was recovered, m. p. and mixed m. p. 120°, after recrystallisation from acetone.

Action of Potassium Thiolacetate on 5 : 6-*Ditoluene-p-sulphonyl* 1 : 3-2 : 4-*Diethylidene Sorbitol*.—The ditoluene-*p*-sulphonate (5 g.) and potassium thiolacetate (4·5 g.) in acetone (100 c.c.) were heated under reflux for 6 hours. On addition of water to the filtered and concentrated solution, a solid (3·5 g.; m. p. 125°) was deposited. Recrystallisation from methanol gave needles of 5-*toluene-p-sulphonyl* 6-*acetyl* 1 : 3-2 : 4-*diethylidene* 6-*thiosorbitol*, m. p. 128°, $[\alpha]_D^{20}$ −23·2° (*c*, 2 in chloroform) (Found: C, 50·9; H, 5·6. $C_{19}H_{26}O_8S_2$ requires C, 51·1; H, 5·85%). Light absorption: max. 2260 A., ε 21,000. This compound (1 g.) was recovered unchanged, m. p. and mixed m. p. 128°, after being heated with potassium thiolacetate (0·5 g.) in acetone (25 c.c.) at 110° for 15 hours.

Action of Potassium Thiolacetate on 5 : 6-*Dimethanesulphonyl* 1 : 3-2 : 4-*Diethylidene Sorbitol*.—The dimethanesulphonate (1 g.) and potassium thiolacetate (1·2 g.) in acetone (25 c.c.) were heated under reflux for 6 hours. Only 0·05 g. of a dark water-insoluble product was obtained. With a shorter time of reaction (1 hour) a dark oil (0·7 g.) was isolated, but it appeared to contain much unchanged starting material.

Non-interaction of Potassium Thiolacetate and Phenyl Toluene-p-sulphonate.—The toluene-*p*-

sulphonate (1 g.), potassium thiolacetate (0·9 g.), and acetone (50 c.c.) were heated at 110° for 18 hours. Unchanged starting material (0·9 g.) was obtained, having m. p. 93°, raised to 95° on recrystallisation from ethanol.

Action of Potassium Thiolacetate on the Isomeric Toluene-p-sulphonate–Benzoates of Propane-1 : 2-diol.—(i) The material of m. p. 79° (5 g.) and potassium thiolacetate (3·5 g.) in acetone (50 c.c.) were heated under reflux for 1 hour; a quantity of potassium toluene-*p*-sulphonate was formed during this time. The cooled mixture was filtered, and the filtrate was concentrated to 10 c.c. and diluted with water, whereupon a semi-solid product was precipitated. This was collected, and on recrystallisation from methanol it gave the 2-toluene-*p*-sulphonate 1-benzoate of propane-1 : 2-diol, identical (m. p. and mixed m. p. 105°) with that described above. Evaporation of the mother-liquors from the crystallisation gave an oil, which on distillation furnished 2-*benzoyloxypropyl* 1-*thiolacetate* (1·2 g.), b. p. 122°/1 mm., n_D^{20} 1·5328 (Found: C, 60·8; H, 6·2. $C_{12}H_{14}O_3S$ requires C, 60·45; H, 5·9%); a small non-volatile residue consisted mainly of the compound, m. p. 105°. Treatment of the thiolacetate (0·1 g.) in ethanol (10 c.c.) with 1-chloro-2 : 4-dinitrobenzene (0·085 g., 1 mol.) and 10% aqueous sodium hydroxide (0·35 c.c., 2 mol.) under reflux for 10 minutes, followed by dilution with water, gave a precipitate of 2 : 4-*dinitrophenyl* 2-*benzoyloxypropyl sulphide*, which formed yellow needles (0·1 g.), m. p. 139°, from ethanol (Found: N, 7·75. $C_{18}H_{16}O_6N_2S$ requires N, 7·75%); the same product was obtained when the amount of sodium hydroxide was increased to 3 mols., indicating the resistance of the secondary benzoyl group towards hydrolysis under these conditions (compare the primary isomer, below).

(ii) The compound, m. p. 105° (3 g.), was recovered unchanged (2·9 g.) after being heated with potassium thiolacetate (2·1 g.) and acetone (50 c.c.) under reflux for 1 hour. The same mixture was therefore heated in a sealed tube at 110° for 15 hours, and gave 1-*benzoyloxypropyl* 2-*thiolacetate* (1·2 g.), b. p. 118°/1 mm., n_D^{20} 1·5248 (Found: C, 60·8; H, 6·05. $C_{12}H_{14}O_3S$ requires C, 60·45; H, 5·9%). When this compound (0·1 g.) was heated under reflux for 10 minutes in ethanol (10 c.c.) with 1-chloro-2 : 4-dinitrobenzene (0·085 g.) and 10% aqueous sodium hydroxide (0·53 c.c., 3 mols.), the subsequent addition of water gave 2 : 4-*dinitrophenyl* 2-*hydroxyisopropyl sulphide*, which crystallised from aqueous ethanol as pale yellow needles, m. p. 87° (Found: N, 10·9. $C_9H_{10}O_5N_2S$ requires N, 10·85%).

Light-absorption data were kindly determined by Dr. E. A. Braude.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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111. *Dithiols. Part V. Further Non-vicinal Dithiols.*

By PETER BLADON and L. N. OWEN.

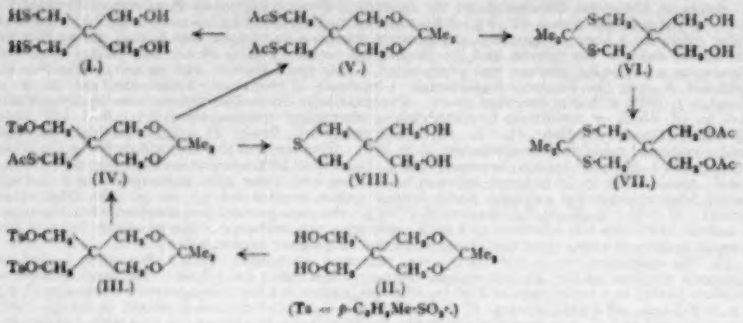
The sulphonyloxy–thiolacetate exchange reaction (Chapman and Owen, preceding paper) has been applied to the preparation of dithiopentaerythritol, 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (*dithicisomannide*), and 1 : 6-*dithiomannitol*. Two unexpected instances of the fission of an *iso*propylidene group have been encountered in some derivatives of pentaerythritol. The formation of a cyclic sulphide, by removal of the toluene-*p*-sulphonyl group from a 1-tosyl-3-acetylthio-compound, is recorded.

DITHIOPENTAERYTHRITOL (I) was first prepared by Backer and Tamsma (*Rec. Trav. chim.*, **1938**, **57**, 1183) by interaction of pentaerythritol dibromohydrin with sodium disulphide, followed by reduction of the intermediate cyclic disulphide with sodium in liquid ammonia. Peppel and Signaigo (U.S.P. 2,402,665) used a similar method, but reduced the disulphide by hydrogenation under pressure over a cobalt polysulphide catalyst.

It was thought that a more convenient laboratory method for the preparation of (I) could be based on the sulphonyloxy–thiolacetate exchange reaction described by Chapman and Owen (Part IV; preceding paper), since suitable starting materials are readily obtained by protection of two of the hydroxyl groups in pentaerythritol by the formation of cyclic acetals, either with aldehydes (Read, *J.*, **1912**, **101**, 2090; Schulz and Tollens, *Annalen*, **1890**, **289**, 28; Skrabal and Kalpasanoff, *Ber.*, **1928**, **61**, 55; Böeseken and Felix, *Ber.*, **1928**, **61**, 787; Fairbourne and Woodley, *J.*, **1926**, 3240) or with ketones (Böeseken, *Rec. Trav. chim.*, **1922**, **41**, 722; Skrabal and Zlatewa, *Z. physikal. Chem.*, **1926**, **119**, 305; Böeseken and Hermans, *Ber.*, **1922**, **55**, 3760; Böeseken and Felix, *Ber.*, **1929**, **62**, 1310; Orthner, *Ber.*, **1928**, **61**, 116). It is necessary to remove the protecting groups at a later stage in the synthesis, and since the cyclic acetals with ketones appear to be more readily hydrolysed than those with aldehydes (Skrabal and Zlatewa, *loc. cit.*), the *iso*propylidene derivative (II) was chosen, and was prepared by a modification of Orthner's method (*loc. cit.*).

Treatment of (II) with two moles of toluene-*p*-sulphonyl chloride in pyridine afforded *ditosyl* iso*propylidene pentaerythritol* (III). Similarly, with methanesulphonyl chloride in pyridine, *dimethanesulphonyl* iso*propylidene pentaerythritol* was formed. Throughout this work, Tipson's general method (*J. Org. Chem.*, **1944**, **9**, 235) has been followed for the preparation of tosyl and methanesulphonyl compounds; he pointed out that it is essential in many cases to

keep the temperature of the reaction mixture below 5°, and in this connection it is of interest that Rapoport (*J. Amer. Chem. Soc.*, 1946, **68**, 341; U.S.P. 2,441,595) found that monoiso-



propylidene pentaerythritol with toluene-*p*-sulphonyl chloride in warm pyridine gave the corresponding dichloro-compound instead of the ditoluene-*p*-sulphonate.

When the ditosyl compound was refluxed with potassium thiolacetate in acetone for a limited time, only one of the tosyloxy-groups was replaced, and O-*tosyl* S-*acetyl* OO-iso*propylidene monothiopentaerythritol* (IV) was obtained. Prolonged treatment of this product with potassium thiolacetate and acetone gave *di*-S-*acetyl* OO-iso*propylidene dithiopentaerythritol* (V). The same compound was obtained by reaction of the dimethanesulphonate with potassium thiolacetate in boiling ethanol.

An attempt was made to remove simultaneously the acetyl and *iso*propylidene residues in (V) by hydrolysis with hot aqueous methanolic hydrogen chloride. The main product, which separated from the reaction mixture, was a high-melting solid containing no free thiol; furthermore, it showed no selective light absorption in the ultra-violet and was therefore not a thiolacetate. It was identified as *SS-iso*propylidene dithiopentaerythritol (VI), previously prepared by Backer and Tamsma (*loc. cit.*). Evaporation of the mother-liquors gave some dithiopentaerythritol (I). The *iso*propylidene compound (VI) may be formed either by reaction of the dithiol with acetone liberated during the hydrolysis, or by hydrolysis of the acetyl groups in (V), followed by direct migration of the acetone residue (possibly through an intermediate *OS-iso*propylidene compound). The mechanism of this reaction will be investigated further, but it may be pointed out that the migration of *iso*propylidene residues in certain dulcitol derivatives, catalysed by quinoline hydrochloride, has been observed by Hann, Maclay, and Hudson (*J. Amer. Chem. Soc.*, 1939, **61**, 2432). In accordance with the known stability of the cyclic acetals of dithiols, (VI) was unaffected by acid hydrolysis.

When the bisacetylthio-compound (V) was hydrolysed with methanolic potassium hydroxide, it gave a small yield of *SS-iso*propylidene dithiopentaerythritol (VI), identical with the material obtained by acid hydrolysis. This result was quite unexpected, since *iso*propylidene residues are normally unaffected by alkali.

*SS-iso*Propylidene dithiopentaerythritol (VI) was characterised by acetylation to yield *di*-O-*acetyl* SS-iso*propylidene dithiopentaerythritol* (VII), isomeric with (V), and by reaction with methanesulphonyl chloride in pyridine to yield *di*-O-*methanesulphonyl* SS-iso*propylidene dithiopentaerythritol*, both derivatives being crystalline. Acetylation of dithiopentaerythritol gave a liquid *tetra-acetate*.

Treatment of tosyl *S*-acetyl *iso*propylidene monothiopentaerythritol (IV) with sodium methoxide in methanol–chloroform (the usual conditions for the formation of anhydro-compounds in the carbohydrate field; cf. Peat and Wiggins, *J.*, 1938, 1088) resulted in elimination of sodium toluene-*p*-sulphonate and of the *iso*propylidene residue, with formation of a small amount of **3 : 3-*bishydroxymethylthietan*** (VIII). The reaction thus provided another example of the unexpected loss of an *iso*propylidene group; as far as we are aware, it is also the first occasion on which a cyclic sulphide has been prepared by such a method.

During the general investigation of the sulphonyloxy-thiolacetate exchange reaction (Part IV; *loc. cit.*) it was found that secondary groups differed considerably amongst them-

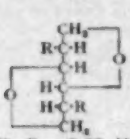
selves in their reactivity. Since, however, it had been shown by Hockett, Fletcher, Sheffield, Goepp, and Soltzberg (*J. Amer. Chem. Soc.*, 1946, **68**, 930) that the two secondary toluene-*p*-sulphonyloxy-groups in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydromannitol were capable of being replaced by iodine when the compound was treated with sodium iodide in acetone at 120°, it appeared probable that an interchange with potassium thiolacetate could be effected; the compound actually used was the 2 : 5-dimethanesulphonate (IX) (Montgomery and Wiggins, *J.*, 1948, 2204), which reacted with potassium thiolacetate in ethanol at 110° to give solid *diacetyl* 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (X), together with much uncrystallisable material. Some deacetylation appeared to occur during the reaction, and the crude product was therefore re-acetylated before being worked up. The thiolacetate (X) was smoothly deacetylated by heating with methanolic hydrogen chloride, and gave 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (XI) as a low-melting solid; it was characterised as the *bis*-2 : 4-*dinitrophenyl* derivative (XII), which showed a remarkably high optical rotation in nitrobenzene solution ($[\alpha]_D^{20}$ −398°).

A second possible route to dithio*iso*mannide was explored. This was based on an observation by Freudenberg and Wolf (*Ber.*, 1927, **60**, 232), who found that the 3-methyl xanthate of di*iso*propylidene glucose, when heated to 300°, underwent a rearrangement and gave a dithiolcarbonate, from which 3-thioglucose was obtained by hydrolysis:

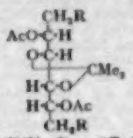
R·O·CS·SMe ⟶ R·S·CO·SMe ⟶ R·SH (R = di*iso*propylidene glucose residue)

Treatment of 1 : 4-3 : 6-dianhydromannitol with sodium in liquid ammonia gave the disodium derivative which, by the action of carbon disulphide, followed by methyl iodide, was converted into the 2 : 5-*di*(*methyl xanthate*) of *iso*mannide (XIII). This, however, failed to undergo any rearrangement on distillation at 170°, since a portion of the product, on hydrolysis, gave *iso*mannide; when it was heated at 290°, extensive decomposition occurred, but the distillate still appeared to consist mainly of unchanged xanthate.

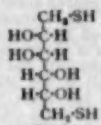
In Part III (Evans, Fraser, and Owen, *J.*, 1949, 248) the preparation of 1 : 6-dithiomannitol was described. Since this compound exhibited some unusual physiological effects, its synthesis by an application of the sulphonyloxy–thiolacetate exchange reaction was devised as a possibly more convenient route. The starting material was 1 : 6-ditosyl 2 : 5-diacetyl 3 : 4-*iso*propylidene mannitol (XIV) (Wiggins, *J.*, 1946, 386). On treatment with potassium thiolacetate in



(IX; R = O·SO$_2$·Me.)
(X; R = SAc.)
(XI; R = SH.)
(XII; R = S·C$_6$H$_3$(NO$_2$)$_2$-)
(XIII; R = O·CS·SMe.)



(XIV; R = OTs.)
(XV; R = SAc.)



(XVI.)

boiling acetone this gave 1 : 2-5 : 6-*tetra-acetyl* 3 : 4-*isopropylidene* 1 : 6-*dithiomannitol* (XV). Removal of the acetyl and *iso*propylidene groups by acid hydrolysis then gave a crude dithiol, which when purified by acetylation afforded crystalline *hexa-acetyl* 1 : 6-*dithiomannitol*. This compound, however, was not identical with the hexa-acetate described by Evans, Fraser, and Owen (*loc. cit.*); furthermore, on deacetylation with methanolic hydrogen chloride it gave pure 1 : 6-*dithiomannitol* (XVI), which differed from the dithiol previously described under this name. This discrepancy led to a reinvestigation of the "dithiomannitol" prepared by the earlier route, and has resulted in the discovery that the original dithiol, its hexa-acetate, and the 1 : 6-dibromide from which it was derived, have the dulcitol configuration (see Bladon, Owen, Overend, and Wiggins, *Nature*, 1949, **164**, 567).

Experimental.

(Light-absorption measurements, in ethanol, were kindly determined by Dr. E. A. Braude.)

*iso*Propylidene *Derivatives of Pentaerythritol.*—Finely powdered pentaerythritol (180 g.) was stirred vigorously with a mixture of acetone (2 l.), water (670 c.c.), and concentrated hydrochloric acid (80 c.c.) for 15 hours. Unchanged pentaerythritol (81·5 g.) was filtered off and washed with acetone. The filtrate was stirred with potassium carbonate (500 g.), added in small portions, and the lower, aqueous

layer was removed and extracted once with ether–acetone (1:1; 500 c.c.). The combined acetone–ether solution was dried by stirring with potassium carbonate (500 g.) for ½ hour, and was then filtered and evaporated. The residue (74 g.), after being dried by distillation with benzene and alcohol under reduced pressure, was powdered and extracted (Soxhlet) with light petroleum (b. p. 40—60°) for ½ hour. Evaporation of this extract gave crude di*iso*propylidene pentaerythritol (4·4 g.), b. p. 160—170° (bath)/30 mm., m. p. 105—111°. The monoisopropylidene derivative (58·3 g.) was obtained by exhaustive extraction of the residue with ether in the same apparatus (24 hours); the m. p., 120—125°, was not changed by recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°). A residue (5·1 g.), m. p. >150°, probably unchanged pentaerythritol, remained after the ether extraction.

For the mono- and di-*iso*propylidene derivatives, respectively, Orthner (*loc. cit.*) gives m. p. 128—129° and 117—117·5°; Skrabal and Kalpaanoff (*loc. cit.*) give 135° and 116°; Rapoport (*loc. cit.*) gives 126—127° for the mono-compound.

Ditosyl iso*Propylidene Pentaerythritol* (III).—The monoisopropylidene compound (17·6 g.) in dry pyridine (150 c.c.) was treated with toluene-*p*-sulphonyl chloride (42 g., 10% excess), the temperature being kept below 5°. After 12 hours at 0°, water (700 c.c.) was slowly added, and the precipitated solid (m. p. 140—146°) was collected and washed with water. Recrystallisation from acetone gave colourless needles (34·6 g., 71%) of *ditosyl* iso*propylidene pentaerythritol*, m. p. 152—153° (Found: C, 54·4; H, 5·9; S, 13·2. $C_{22}H_{28}O_8S_2$ requires C, 54·2; H, 5·8; S, 13·2%).

Dimethanesulphonyl iso*Propylidene Pentaerythritol*.—The monoisopropylidene compound (17·6 g.) was added in small portions to a cooled solution of methanesulphonyl chloride (25·2 g., 10% excess) in dry pyridine (100 c.c.), the temperature being kept below 10°. After being kept overnight at 0°, the mixture was poured into water (400 c.c.). The brown solid was collected, washed with water, and recrystallised from methanol to give *dimethanesulphonyl* iso*propylidene pentaerythritol* (17·9 g.), m. p. 107—110°, raised on further recrystallisation to 110—112° (Found: C, 35·9; H, 6·5; S, 19·35. $C_{10}H_{20}O_8S_2$ requires C, 36·1; H, 6·1; S, 19·3%).

Reaction of Ditosyl iso*Propylidene Pentaerythritol with Potassium Thiolacetate*.—The ditosyl compound (34·5 g., 0·0895 mol.), potassium thiolacetate (20·3 g., 0·178 mol.), and pure acetone (180 c.c.) were heated under reflux for 8 hours, a further quantity of potassium thiolacetate (4 g., 0·035 mol.) being added after 6 hours. The reaction mixture was cooled and filtered, and the salts were well washed with acetone. The filtrate was evaporated, and the residue was treated with water (50 c.c.) and extracted thrice with chloroform (50 c.c. portions). Evaporation of the dried (Na_2SO_4) extracts gave a residue (26·5 g.) which was dissolved in methanol and kept overnight at 0°. The solid (18·7 g.; m. p. 85—92°) was collected and recrystallised from methanol to give O-*tosyl* S-*acetyl* OO-iso*propylidene monothiopentaerythritol* (IV), m. p. 91—93° (Found: C, 52·85; H, 6·4; S, 16·3. $C_{15}H_{20}O_6S_2$ requires C, 52·55; H, 6·2; S, 16·5%). The compound was unstable and underwent extensive decomposition after storage for a few months. Concentration of the methanolic mother-liquors gave further crops of solid, m. p. 55—60°, which probably contained the bisthiolacetate (see below).

Reaction of Tosyl S-*Acetyl* OO-iso*Propylidene Monothiopentaerythritol with Potassium Thiolacetate*.—The above monotosyl compound (7·76 g.), potassium thiolacetate (6·8 g., large excess), and acetone (70 c.c.) were heated under reflux for 30 hours. The precipitated solid was filtered off and well washed with acetone. The filtrates were evaporated to small bulk, the residue was treated with water, and the oil was isolated by chloroform extraction followed by evaporation of the dried (Na_2SO_4) extracts. Crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) failed to give any pure material; apparently the bisthiolacetate and the monotosyl-monothiolacetate form a mixture, m. p. 57—59°, which is not readily separable by crystallisation. Accordingly, the crude product was distilled, b. p. 120° (bath)/0·0001 mm., and the solid distillate (3·95 g., 67·5%) was recrystallised from methanol. *Di-S-acetyl* OO-iso*propylidene dithiopentaerythritol* (V) formed colourless tablets, m. p. 63—65° (Found: C, 49·7; H, 7·3; S, 22·15. $C_{12}H_{20}O_4S_2$ requires C, 49·3; H, 6·9; S, 21·9%). Light absorption: max. 2290 A., ε 8500.

Reaction of Dimethanesulphonyl iso*Propylidene Pentaerythritol with Potassium Thiolacetate*.—The dimethanesulphonate (17·85 g., 0·054 mol.), potassium thiolacetate (18·5 g., 0·161 mol.), and ethanol (170 c.c.) were heated under reflux for 13 hours. The potassium methanesulphonate (15 g.) was removed and washed with ethanol. The filtrates were concentrated under reduced pressure, then diluted with water and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a syrup (14·9 g., 95%) which crystallised on being stirred with methanol. Recrystallisation from this solvent gave large rectangular tablets of di-S-acetyl *OO-iso*propylidene dithiopentaerythritol (12·0 g., 76%), m. p. 63—65°, undepressed on admixture with the material prepared from the tosyl compound.

Acid Hydrolysis of Di-S-acetyl OO-iso*Propylidene Dithiopentaerythritol*.—The compound (10 g.) was heated under reflux for 2 hours with methanol (20 c.c.) and 2*N*-aqueous hydrochloric acid (20 c.c.) in an atmosphere of nitrogen. Concentration of the solution then gave a solid (4·4 g.), which was collected, washed with water, and recrystallised from dioxan. *SS-iso*Propylidene dithiopentaerythritol (VI) formed flattened needles, m. p. 198—200°, which did not show selective ultra-violet-light absorption or give a thiol reaction (Found: S, 30·7. Calc. for $C_8H_{14}O_2S_2$: S, 30·8%). Backer and Tamama (*loc. cit.*) give m. p. 199·5—200·5°. Further concentration of the original aqueous solution gave a second crop of crystals (1 g.), m. p. 95—97°, and, on complete evaporation, a final residue (1 g.), m. p. 87—89°. Recrystallisation of these from benzene gave plates, m. p. 95—96°, of dithiopentaerythritol (I) (Found: thiol S, 37·9. Calc. for $C_5H_{12}O_2S_2$: S, 38·1%). Acetylation of dithiopentaerythritol with acetic anhydride and sodium acetate at 100° for 8 hours gave the *tetra-acetate* as a colourless oil, b. p. 100—120° (bath)/0·0001 mm., n_D^{15} 1·5092 (Found: C, 46·55; H, 6·2; S, 19·15. $C_{13}H_{20}O_4S_2$ requires C, 46·5; H, 6·0; S, 19·1%). Light absorption: max. 2310 A., ε 8400.

Alkaline Hydrolysis of Di-S-acetyl OO-iso*Propylidene Dithiopentaerythritol*.—The compound (0·93 g.) was kept overnight under nitrogen with potassium hydroxide (1·5 g.) in methanol (15 c.c.). The alkali was then neutralised with carbon dioxide, water added, and the mixture extracted thrice with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a pale yellow oil (0·65 g.) containing free thiol, which on distillation furnished a liquid forerun, b. p. 90—120° (bath)/0·0001 mm., and a semi-solid material

(0·26 g.), b. p. 120—150° (bath)/0·0001 mm. The latter on crystallisation from methanol gave *SS-iso*propylidene dithiopentaerythritol, m. p. and mixed m. p. 197—199°.

*SS-iso*Propylidene dithiopentaerythritol was recovered largely unchanged (64%) after being heated with dioxan–5*N*-hydrochloric acid (1 : 1) for 4 hours on the steam-bath, followed by dilution with water; the aqueous filtrate gave only a faintly positive thiol test with nitroprusside and alkali.

The *diacetate* (VII), m. p. 71—72° after recrystallisation from methanol, was prepared by heating the compound with acetic anhydride and sodium acetate on the steam-bath for 6 hours (Found: C, 49·6; H, 7·0; S, 21·85. $C_{11}H_{18}O_4S_2$ requires C, 49·3; H, 6·9; S, 21·9%).

The *dimethanesulphonate* was prepared by treatment of *SS-iso*propylidene dithiopentaerythritol with a slight excess of methanesulphonyl chloride in pyridine for 12 hours at 0°; it formed fine needles, m. p. 123—125°, from acetone–methanol (Found: C, 33·2; H, 5·6; S, 35·2. $C_{10}H_{20}O_6S_4$ requires C, 32·9; H, 5·5; S, 35·2%).

Reaction of Tosyl S-*Acetyl* OO-*isoPropylidene Monothiopentaerythritol with Sodium Methoxide.*—The tosyl compound (1·94 g.) in chloroform (5 c.c.) was treated at 0° with sodium (0·14 g.) in dry methanol (3 c.c.). Sodium toluene-*p*-sulphonate rapidly separated, at first as a gel, and subsequently in crystalline form. The mixture was kept for an hour at room temperature, and at 0° overnight. Water (15 c.c.) was then added, and the chloroform layer was separated; the aqueous solution was extracted thrice more with chloroform. The dried (Na_2SO_4) extracts were evaporated and the residue was brought to crystallisation by evaporation several times with light petroleum (b. p. 40—60°). Crystallisation from methanol gave a small amount (0·19 g.) of ditosyl *iso*propylidene pentaerythritol, m. p. and mixed m. p. 152—154°, presumably present as impurity in the starting material. The mother-liquors were evaporated, and the residue was heated under reduced pressure; 3 : 3-*bishydroxymethylthietan* (VIII) (54 mg.), m. p. 72—74°, sublimed at 90—120° (bath temp.)/0·01 mm. (Found: C, 44·8; H, 7·5; S, 24·1. $C_4H_{10}O_2S$ requires C, 44·8; H, 7·5; S, 23·9%). A considerable amount of viscid non-volatile material probably consisted of polymer.

1 : 4-3 : 6-*Dianhydromannitol* (cf. Hockett *et al.*, *loc. cit.*; Montgomery and Wiggins, *J.*, 1947, 433).—Mannitol (50 g.) and toluene-*p*-sulphonic acid (5 g.) were thoroughly mixed by shaking in a 400-c.c. Claisen flask, fitted with the usual capillary leak and thermometer, and connected to a cooled receiver. The pressure was reduced to 50 mm., and the mixture was heated to 160—180° till molten. The bath temperature was then reduced to 140—150° and kept thereat for 1 hour whilst water was collected in the receiver. The pressure was then reduced to 2 mm., and as much material as possible was distilled into a clean receiver at a bath temperature of 160—200°, care being taken, particularly towards the end of the distillation, to keep the frothing under control. The pale yellow distillate, b. p. 120—130°/2 mm. (12·9 g.), crystallised on being seeded with *iso*mannide, and after recrystallisation from the minimum amount of ethyl acetate it formed prisms (10·5 g., 26%), m. p. 85—86°. The preparation was successfully carried out on twice this scale.

Diacetyl 2 : 5-*Dithio*-1 : 4-3 : 6-*dianhydromannitol* (X).—2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (Montgomery and Wiggins, *J.*, 1948, 2204) (6·0 g.), potassium thiolacetate (6·9 g.; excess), and thiolacetic acid (0·2 c.c.) in ethanol (30 c.c.) were heated in a sealed tube at 110—115° for 12 hours. The precipitated potassium methanesulphonate (5·5 g.; calc., 5·4 g.) was removed, and the alcoholic filtrates were evaporated to dryness. The residue was acetylated by heating with acetic anhydride (20 c.c.) and fused sodium acetate (2 g.) for 2 hours on the steam-bath, in order to counteract any deacetylation which might have occurred during the initial reaction. The resulting mixture was stirred with water to decompose the excess of acetic anhydride, and the oil was isolated by 4 extractions with chloroform (35 c.c.; 3 × 15 c.c.). The extracts were washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to a red oil (6·3 g.) which was fractionally distilled in nitrogen. After removal of some low-boiling material, the main product was collected at 135—140°/0·1 mm. (bath temp. 190—200°), n_D^{17} 1·553—1·552; on storage, it solidified. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave prisms, m. p. 35—37°; yield 3·25 g. (62%). Further recrystallisation from the same solvents gave colourless crystals, m. p. 36—37·5°, $[\alpha]_D^{17}$ +19·2° (*c*, 2·2 in chloroform), of *diacetyl* 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (Found: C, 46·1; H, 5·65; S, 24·55. $C_{10}H_{14}O_4S_2$ requires C, 45·8; H, 5·4; S, 24·45%). Light absorption: max. 2310 A., ε 8400.

2 : 5-*Dithio*-1 : 4-3 : 6-*dianhydromannitol* (XI).—The above diacetyl compound (3·12 g.) was heated under reflux with 2·5% hydrogen chloride in methanol (50 c.c.) for 4 hours. The solvent was removed by distillation under reduced pressure and the residual oil (2·12 g., 100%) was kept under reduced pressure over potassium hydroxide, whereupon it partly solidified. Distillation furnished 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* as a pale yellow oil, m. p. 15—16°, b. p. 60—80° (bath)/0·0001 mm., n_D^{17} 1·5692, $[\alpha]_D^{18}$ +65° (*c*, 2·5 in chloroform), $[\alpha]_D^{20}$ +120° (*c*, 1·4 in 0·2*N*-aqueous sodium hydroxide) (Found: C, 40·6; H, 5·75; S, 36·1; thiol S, 36·4. $C_6H_{10}O_3S_2$ requires C, 40·4; H, 5·65; S, 36·0%). The dithiol was readily soluble in all the common organic solvents.

Bis-2 : 4-*dinitrophenyl Derivative* (XII).—The dithiol (0·26 g.) was heated under reflux with 2 : 4-dinitrochlorobenzene (0·6 g.) and potassium hydroxide (0·17 g.) in ethanol (10 c.c.) for 1 hour. A copious precipitate of potassium chloride was produced. On pouring the solution into water, an emulsion was obtained, but this was broken on acidification with dilute sulphuric acid. The brown precipitate was collected, washed with water, and dried; yield, 0·73 g. (98%); m. p. 145—150°. One recrystallisation from aqueous acetic acid, and three from acetone gave the *derivative* as yellow needles, m. p. 187—188°, $[\alpha]_D^{19}$ −398° (*c*, 1 in nitrobenzene) (Found: C, 41·9; H, 3·0; N, 11·1. $C_{18}H_{14}O_{12}N_4S_2$ requires C, 42·35; H, 2·8; N, 11·0%). The substance was difficultly soluble in most common solvents, but dissolved readily in hot acetic acid or acetone.

1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di*(*methyl Xanthate*) (XIII).—1 : 4-3 : 6-Dianhydromannitol (7·3 g.) in liquid ammonia (300 c.c.) was treated with finely divided sodium (2·3 g.). After a few minutes, during which the blue colour had not entirely disappeared, the ammonia was allowed to evaporate, and the last traces were removed from the residue by heating under reduced pressure on the steam-bath. The fine white powder was heated under reflux with carbon disulphide (80 c.c.) for 22 hours. Methyl iodide (43 g.) was then added, and the heating continued for a further 16 hours. The mixture was

shaken with water (100 c.c.), and the lower aqueous layer was separated and extracted thrice with ether (100-c.c. portions). The combined carbon disulphide and ethereal solutions were dried (Na_2SO_4) and evaporated. The deep-red residue (12·2 g.) on distillation from a wide-necked retort under high vacuum gave some very volatile material (possibly dimethyl *iso*mannide) which condensed in the liquid-air trap. The second fraction (0·43 g.), b. p. <120° (bath)/0·0001 mm., n_D^{25} 1·6387, $[\alpha]_D^{25}$ +159° (*c*, 2·3 in chloroform), probably consisted mainly of monomethyl *iso*mannide mono(methyl xanthate). After the collection of some intermediate fractions (2·8 g.), the main bulk (6·2 g.) distilled at 170° (bath)/0·0001 mm. Redistillation gave the *di(methyl xanthate)* as a viscous orange liquid, n_D^{25} 1·6318, $[\alpha]_D^{25}$ +266° (*c*, 2·6 in chloroform) (Found: C, 36·6; H, 4·5; S, 39·3. $C_{10}H_{14}O_4S_4$ requires C, 36·8; H, 4·3; S, 39·3%). Light absorption: max. 2280, 2800 A.; ε 10,100 and 14,000, respectively. After being kept for several weeks, the syrup crystallised. Two recrystallisations from ethyl acetate–methanol afforded pale yellow plates, m. p. 58—60°, $[\alpha]_D^{25}$ +274° (*c*, 2·0 in chloroform) (Found: C, 37·0; H, 4·5; S, 39·3%). Light absorption: max. 2270, 2800 A.; ε 14,500 and 17,500; infl. 2730 A.; ε 15,000.

Reaction of 1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di(methyl Xanthate) with Sodium Methoxide.*—The above compound (1 g.; a syrup) was heated under reflux for 4 hours with sodium methoxide (1 g.) in methanol (15 c.c.). The alkali was then neutralised with carbon dioxide, the solution was filtered, and the filtrate and washings were evaporated to dryness. The crystalline residue was extracted overnight in a Soxhlet apparatus with chloroform; evaporation of these extracts gave *iso*mannide (0·43 g.), which was characterised by conversion into the dimethanesulphonyl derivative, m. p. and mixed m. p. 101—102°, $[\alpha]_D^{25}$ +134° (*c*, 1 in chloroform).

Pyrolysis of 1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di(methyl Xanthate).*—A portion of the syrup (1·2 g.) was heated at 290° at atmospheric pressure in a small retort held vertically in a metal-bath. Under these conditions, the compound refluxed gently, and slowly evolved a small amount of volatile material which collected in a liquid-air trap attached to the end of the retort. The temperature was allowed to fall to 250° during one hour, and the retort was then rearranged for distillation in the usual way. A small quantity (0·06 g.) of an oil was collected at 120—125° (bath)/0·0001 mm., which probably consisted of unchanged xanthate; light absorption: max. 2260, 2810 A., $E_{1\,cm}^{1\%}$ 240, 220; infl. 2870 A., $E_{1\,cm}^{1\%}$ 160. A considerable amount of dark viscous material remained in the retort.

1 : 2·5 : 6-*Tetra-acetyl* 3 : 4-*iso*Propylidene 1 : 6-*Dithiomannitol* (XV).—1 : 6-Ditosyl 2 : 5-diacetyl 3 : 4-*iso*propylidene mannitol, m. p. 111—113°, $[\alpha]_D^{25}$ +22·9° (*c*, 1·7 in chloroform) was prepared by Wiggins's method (*J.*, 1946, 384). This substance (8 g.), potassium thiolacetate (4·5 g.), and dry acetone (30 c.c.) were heated under reflux for 4 hours. Precipitated potassium toluene-*p*-sulphonate was removed (6·7 g., 102%) and washed with acetone, and the filtrates were concentrated and then diluted with water (30 c.c.). The oily layer was taken up in chloroform, and the aqueous portion was extracted thrice with chloroform. Removal of solvent from the dried (Na_2SO_4) extracts gave the *tetra-acetyl* derivative as a dark viscid oil, which could be distilled only in small quantities, b. p. 120° (bath)/0·0001 mm., n_D^{25} 1·4950, $[\alpha]_D^{25}$ +114° (*c*, 1·4 in chloroform) (Found: C, 47·6; H, 6·4; S, 14·9. $C_{18}H_{28}O_8S_2$ requires C, 48·35; H, 6·2; S, 15·2%). Light absorption: max. 2280 A., ε 8000.

1 : 6-*Dithiomannitol* (XVI).—The above bisthiolacetate (5·6 g.; not distilled) was heated under reflux for 5 hours with 2% methanolic hydrogen chloride in an atmosphere of nitrogen. The solvent was then removed under reduced pressure, but the residual glass could not be induced to crystallise, and possibly contained some partly hydrolysed material. It was therefore heated for a further 5 hours with 2*N*-hydrochloric acid (7 c.c.) at 100°, under nitrogen. Freeze-drying of the solution at *ca.* 0° under reduced pressure then gave the crude dithiol (2·7 g.) as a powder, m. p. 120—135°, $[\alpha]_D^{25}$ +18° (*c*, 1·2 in water) (Found: thiol S, 24·4. $C_6H_{14}O_4S_2$ requires S, 29·9%), which was acetylated by being heated on the steam-bath for 5 hours with acetic anhydride (12 c.c.) and fused sodium acetate (1 g.). The reaction mixture was then stirred with water and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue from methanol gave needles (0·6 g.) of *hexa-acetyl* 1 : 6-*dithiomannitol*, m. p. 107—109°, $[\alpha]_D^{25}$ +81·8° (*c*, 1 in chloroform), raised on further recrystallisation from methanol to m. p. 109—111°, $[\alpha]_D^{25}$ +85° (*c*, 1 in chloroform) (Found: C, 46·5; H, 5·9; S, 13·65. $C_{18}H_{30}O_{10}S_2$ requires C, 46·3; H, 5·6; S, 13·7%). Light absorption: max. 2300 A., ε 8200.

Deacetylation of the hexa-acetate (0·59 g.) by heating under reflux with 2% methanolic hydrogen chloride for 5 hours, followed by evaporation to dryness under reduced pressure, gave a solid (0·3 g.), which was freed from traces of acid by being kept under reduced pressure for several hours over potassium hydroxide. Recrystallisation from methanol gave 1 : 6-*dithiomannitol*, m. p. 155—157°, $[\alpha]_D^{25}$ +1·96° (*c*, 0·6 in water), $[\alpha]_D^{25}$ +15° (*c*, 0·6 in 2·9% aqueous borax) (Found: C, 34·3; H, 6·85; S, 29·4; thiol S, 28·7. $C_6H_{14}O_4S_2$ requires C, 33·6; H, 6·6; S, 29·9%). The dithiol is hygroscopic, and recrystallisation is attended with some difficulty. Unlike 1 : 6-dithiodulcitol (the former "1 : 6-dithiomannitol"), it is readily soluble in water.

1 : 2·3 : 4-*Diisopropylidene* 1 : 4-*Dithioerythritol.*—In Part III (Evans, Fraser, and Owen, *loc. cit.*) the m. p. of this substance was erroneously given as 145°; it has m. p. 105°.

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Imperial College of Science and Technology,
S. Kensington, London, S.W.7.

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112. *Dithiols. Part VI. Ethers of 2 : 3-Dimercaptopropanol with Mannitol and Sorbitol.*

By Peter Bladon and L. N. Owen.

A description is given of experiments directed towards the synthesis of the following water-soluble ethers of "BAL" (2 : 3-dimercaptopropanol): 1- and 3-(2 : 3-dimercaptopropyl) mannitol; 6-(2 : 3-dimercaptopropyl) sorbitol; and 2-(2 : 3-*dimercaptopropyl*) 1 : 4-3 : 6-*di-anhydromannitol*. The *acetyl* derivatives were obtained in each case.

In Part II of this series (Evans and Owen, *J.*, 1949, 244), the preparations of the α- and β-glyceryl ethers of "BAL" (2 : 3-dimercaptopropanol) were described. This work has now been extended to the synthesis of compounds in which the hydroxyl group of "BAL" is etherified by one of the hydroxyl groups of mannitol or sorbitol. The general method was the same as in the earlier work, and involved the preparation of the corresponding fully acetylated allyl ethers. These were made by three general methods:

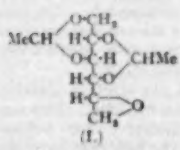
(*a*) Direct allylation of a suitably protected derivative of the hexitol with allyl bromide in the presence of sodium hydroxide. This method has been studied by Yanovsky and his co-workers (*J. Amer. Chem. Soc.*, 1944, **66**, 1625; 1945, **67**, 46), who applied it to the complete allylation of carbohydrates. In the present work, it was necessary to allylate only one of the two hydroxyl groups usually available in the protected hexitols, and the procedure adopted was therefore the addition of allyl bromide to a solution of the hexitol derivative in concentrated aqueous sodium hydroxide.

(*b*) Reaction of the sodium derivative of the hydroxy-compound (prepared by treatment with sodium in liquid ammonia) with allyl bromide.

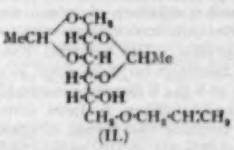
(*c*) Ring-opening of an ethylene oxide anhydro-compound with sodium allyl oxide in allyl alcohol. In the case of terminal epoxides, ring opening proceeds mainly in such a way that the allyloxy-group becomes attached to the terminal carbon atom (cf. the analogous case of ring opening with sodium methoxide, Vargha and Puskás, *Ber.*, 1943, **76**, 859). No Walden inversion occurs, and the product has the configuration of the initial epoxide. With a non-terminal epoxide, the ring opening can occur in two ways, and, since Walden inversion takes place in both cases, neither of the two products has the configuration of the initial epoxide.

The allyl ethers were then subjected to acid hydrolysis to remove the protecting groups (*iso*propylidene or ethylidene), and then fully acetylated, the products being treated with bromine in carbon tetrachloride solution, to yield the dibromopropyl ethers. These compounds, on treatment with potassium thiolacetate in boiling ethanol, gave the corresponding bisthiol-acetates. Deacetylation of these was carried out with either barium methoxide or methanolic hydrogen chloride.

The starting material for the preparation of the 6-sorbitol ether of 2 : 3-dimercaptopropanol was 1 : 3-2 : 4-diethylidene sorbitol (Appel, *J.*, 1935, 425; Hockett and Nickerson, *J. Amer. Chem. Soc.*, 1947, **69**, 850). Attempts at the direct allylation of this compound with allyl



(I.)



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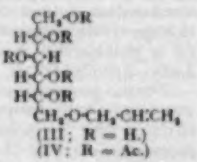


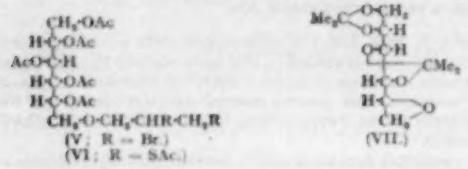
(III; R = H.)
(IV; R = Ac.)

bromide and alkali, aimed at the formation of a monoallyl derivative, gave mixtures of mono- and di-allyl compounds. Accordingly, the route *via* the anhydro-compound was used. 1 : 3-2 : 4-Diethylidene 5 : 6-anhydrosorbitol (I) was prepared by the method of Vargha and Puskás (*loc. cit.*) (see also Sullivan, *J. Amer. Chem. Soc.*, 1946, **67**, 837; Wiggins, *J.*, 1946, 388). An improved yield (93%) was obtained in the conversion of the intermediate 6-tosyl compound into the anhydro-compound. It was also possible to avoid isolation of the tosyl derivative by treatment of the crude syrup with sodium methoxide, and to isolate the anhydro-compound by sublimation, with little alteration in the overall yield.

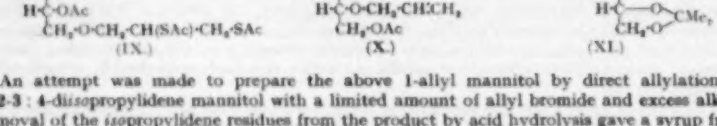
Ring opening of (I) with sodium allyl oxide in allyl alcohol at 100° gave 1 : 3-2 : 4-*diethylidene* 6-*allyl sorbitol* (II). The crude 6-allyl sorbitol (III) obtained by removal of the ethylidene

residues by acid hydrolysis was a syrup, which was acetylated to give *penta-acetyl* **6-*allyl sorbitol*** (IV) as a liquid which could be distilled in a high vacuum.

Addition of bromine to this compound gave *penta-acetyl* **6-(2 : 3-*dibromopropyl*) *sorbitol*** (V), which, on reaction with potassium thiolacetate in boiling ethanol furnished ***hepta-acetyl* 6-(2 : 3-*dimercaptopropyl*) *sorbitol*** (VI). Deacetylation with barium methoxide furnished a crude barium salt of the dithiol, but, as previously found with the barium salt of dimercaptopropylglucoside (cf. Evans and Owen, *J.*, **1949**, **244**), this could not be purified.



For the preparation of 2 : 3-dimercaptopropyl 1(or 6)-mannitol ether, 1 : 2-3 : 4-di*iso*propylidene mannitol was used (Wiggins, *J.*, 1946, 13); this was converted into 1 : 2-3 : 4-di*iso*propylidene 5 : 6-anhydromannitol (VII) by a modification of the method of Wiggins (*J.*, 1946, 388), the intermediate 6-tosyl compound not being isolated, but treated directly, in the crude state, with sodium methoxide; the anhydro-compound was then purified by sublimation. Treatment of (VII) with sodium allyl oxide in boiling allyl alcohol gave ***6-allyl* 1 : 2-3 : 4-di*isopropylidene mannitol***, converted by acid hydrolysis into crystalline ***1(or 6)-allyl mannitol***, acetylation of which gave the solid *penta-acetyl* derivative (VIII). With bromine, this gave ***penta-acetyl* 1-(2 : 3-*dibromopropyl*) *mannitol*** and thence, with potassium thiolacetate, ***hepta-acetyl* 1-(2 : 3-*dimercaptopropyl*) *mannitol*** (IX) was obtained. Deacetylation with barium methoxide gave a crude barium salt.

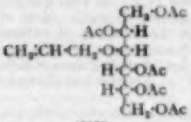


An attempt was made to prepare the above 1-allyl mannitol by direct allylation of 1 : 2-3 : 4-di*iso*propylidene mannitol with a limited amount of allyl bromide and excess alkali. Removal of the *iso*propylidene residues from the product by acid hydrolysis gave a syrup from which 1-allyl mannitol was obtained in small yield. Acetylation of the material remaining in the mother-liquors gave a syrupy product, and determination of the acetyl content and of the unsaturation showed that this was a mixture of mono- and di-allyl compounds. On long storage, crystals separated, and after purification these were found to have the analysis expected for a penta-acetyl monoallyl mannitol. The material was not identical with penta-acetyl 1-allyl mannitol (VIII), and must therefore be ***penta-acetyl* 2(or 5)-*allyl mannitol*** (X).

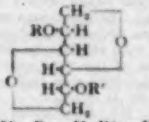
For the projected preparation of 3-(2 : 3-dimercaptopropyl) mannitol, the starting material was 1 : 2-5 : 6-di*iso*propylidene mannitol (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338). This was allylated with 1·4 moles of allyl bromide and excess of alkali, to give ***3-allyl* 1 : 2-5 : 6-di*isopropylidene mannitol*** (XI). Monoallylation in this case is facilitated by the fact that only one monoallyl derivative is possible, since the 3- and the 4-position in mannitol are identical. Acid hydrolysis of (XI) gave crystalline 3-allyl mannitol, the properties of which agreed well with those given by Wrigley and Yanovsky (*J. Amer. Chem. Soc.*, 1948, **70**, 2194) who obtained it as a by-product in the preparation of 3 : 4-diallyl mannitol. It was converted into the *penta-acetyl* derivative (XII) and thence into *penta-acetyl* **3-(2 : 3-*dibromopropyl*) *mannitol***. The corresponding bisthiolacetate was not obtained pure.

The starting material for the preparation of the 2 : 3-dimercaptopropyl ether of 1 : 4-3 : 6-dianhydromannitol was 1 : 4-3 : 6-dianhydromannitol (XIII) itself, which was prepared from mannitol by the methods of Wiggins (*J.*, 1945, 5) and of Bladon and Owen (preceding paper). Attempts at the direct monoallylation of this compound, with allyl bromide and excess of alkali, all yielded mainly the diallyl compound. The method which was finally used involved conversion

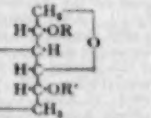
of the dianhydromannitol into its monosodium derivative by treatment with sodium in liquid ammonia, and refluxing of the dry sodium salt with excess of allyl bromide in benzene. A mixture of mono- and di-allyl compounds again resulted, but the proportion of monoallyl compound was considerably higher. The mixture was heated with phthalic anhydride in pyridine (method of Levene and Mikeska, *J. Biol. Chem.*, 1927, **75**, 587), and the reaction product was treated with aqueous sodium carbonate solution; the alkali-insoluble portion consisted of 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol, whilst the alkali-soluble portion, on acidification, gave solid 2-*allyl* 1 : 4-3 : 6-*dianhydromannitol* 5-(*hydrogen phthalate*) (XIV). The diallyl compound had properties agreeing with those described by Gregory and Wiggins (*J.*, 1947, 1405). The hydrogen phthalate on hydrolysis gave 2-*allyl* 1 : 4-3 : 6-*dianhydromannitol* (XV) as a liquid,



(XII).



(XIII; R = H, R′ = H.)
(XIV; R = CH_2·CH:CH_2, R′ = CO·C_6H_4·CO_2H.)
(XV; R = CH_2·CH:CH_2, R′ = H.)
[XVI; R = CH_2·CH(SAc)·CH_2·SAc, R′ = Ac.]
[XVII; R = CH_2·CH(SH)·CH_2·SH, R′ = H.]



(XVIII; R = R′ = H.)
(XIX; R = CH_2·CH:CH_2, R′ = H.)
(XX; R = H, R′ = CH_2·CH:CH_2.)

only slightly more viscous than the diallyl compound and of almost identical boiling point. Acetylation of (XV) gave the *acetyl* derivative, which readily took up bromine in carbon tetrachloride solution to give 5-*acetyl* 2-(2 : 3-*dibromopropyl*) 1 : 4-3 : 6-*dianhydromannitol*; treatment of this with potassium thiolacetate in boiling alcohol gave *triacetyl* 2-(2 : 3-*dimercaptopropyl*) 1 : 4-3 : 6-*dianhydromannitol* (XVI). Finally, almost pure 2-(2 : 3-*dimercaptopropyl*) 1 : 4-3 : 6-*dianhydromannitol* (XVII) was obtained by deacetylation of the thiolacetate with methanolic hydrogen chloride. The free dithiol was a viscid liquid, readily soluble in water.

The analogous allylation of the monosodium derivative of 1 : 4-3 : 6-dianhydrosorbitol (XVIII) (Montgomery and Wiggins, *J.*, 1946, 390) gave, by use of the hydrogen phthalate method of separation, 2 : 5-diallyl 1 : 4-3 : 6-dianhydrosorbitol (Gregory and Wiggins, *loc. cit.*) and a liquid which was probably a mixture of the isomeric 2- (XIX) and 5-allyl 1 : 4-3 : 6-dianhydrosorbitol (XX); this mixture yielded a mixture of the corresponding acetyl derivatives on acetylation. Since the two isomers could not be separated, the synthesis was not carried beyond this stage.

Experimental.

(Light absorptions, in ethanol, were determined by Dr. E. A. Braude.)

1 : 3-2 : 4-*Diethylidene Sorbitol*.—Appel's method of preparation (*J.*, 1935, 425) was slightly modified and applied to sorbitol (500 g.), paraldehyde (500 c.c.), and concentrated hydrochloric acid (170 c.c.). After 8 hours' stirring, the mixture was extracted twice with chloroform (300 c.c., 100 c.c.), and the extracts were washed with 200-c.c. portions of water, 10% aqueous sodium hydroxide (twice), and with water again, and dried ($CaCl_2$). The chloroform and most of the excess of paraldehyde were removed by distillation under reduced pressure. The residual syrup was heated with acetic acid (400 c.c.) and water (400 c.c.) on the steam-bath under reflux and under reduced pressure (*ca.* 150 mm.) for 2 hours, the liberated acetaldehyde being removed by a current of air drawn through a capillary leak. The solution was concentrated under reduced pressure until solid began to separate; dilution with water then precipitated triethylidene mannitol (30—40 g.), m. p. 165—167° (after recrystallisation from ethanol), derived from mannitol present as impurity in commercial sorbitol (cf. Bourne and Wiggins, *J.*, 1948, 1933). Evaporation of the aqueous solution gave a syrup, which was taken up in methanol (250 c.c.), and treated with ether (100 c.c.) and light petroleum (b. p. 40—60°) (50 c.c.). 1 : 3-2 : 4-Diethylidene sorbitol crystallised as a fine powder when the solution was kept at 0° for a few days; yield, 120—170 g.; m. p. 210—214°.

Allylation of 1 : 3-2 : 4-*Diethylidene Sorbitol*.—A mixture of the diethylidene sorbitol (23·5 g., 0·1 mol.), acetone (105 c.c.), sodium hydroxide (32 g.), and water (82 g.) was stirred vigorously in a 1-l. 3-necked flask, fitted with mercury-sealed stirrer, reflux condenser, and dropping-funnel, and surrounded by a water-bath at 70°, whilst a solution of allyl bromide (15 g., 0·125 mol.) in acetone (25 c.c.) was added during 2 hours. Heating and stirring were continued for a further 2 hours, and the condenser was then rearranged for distillation; the water-bath was slowly heated to 100°, whilst a stream of nitrogen was blown through the solution to remove volatile material. The contents of the flask were diluted with water (250 c.c.), and the alkali was partly neutralised with sulphuric acid (16·2 c.c. of concentrated acid in 50 c.c. of water). The reaction product was isolated by 5 extractions with ether (total, 350 c.c.), and the dried (K_2CO_3) extracts were evaporated; distillation of the residue gave 12·3 g. (45%) of a very viscous oil, b. p. 120°/0·005 mm., n_D^{20} 1·4730, $[\alpha]_D^{20}$ −7·5° (*c*, 4 in chloroform), $[\alpha]_D^{20}$ −4·2° (*c*, 4 in ethanol), which was

a mixture of mono- and di-allyl compounds (Found: C, 58·2; H, 8·1. Calc. for $C_{12}H_{22}O_6$: C, 56·9; H, 8·1. Calc. for $C_{15}H_{26}O_6$: C, 61·1; H, 8·8%).

1 : 3-2 : 4-*Diethylidene* 5 : 6-*Anhydrosorbitol*.—6-Tosyl 1 : 3-2 : 4-diethylidene sorbitol was prepared by the method of Vargha and Puskás (*Ber.*, 1943, **76**, 859) and crystallised from ethyl acetate–light petroleum (b. p. 60—80°) (cf. Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837); yield, 32%; m. p. 87—90° (Vargha and Puskás, *loc. cit.*, give m. p. 92°).

1 : 3-2 : 4-Diethylidene 5 : 6-anhydrosorbitol was made by the action of sodium methoxide on the 6-tosyl compound (Vargha and Puskás, *loc. cit.*). The yield of almost pure material (m. p. 129—130°) (93%) was much higher than that obtained by these workers, and by Sullivan (*loc. cit.*) (see also the method of preparation given by Wiggins, *J.*, 1946, 388). The anhydro-compound was also made, in almost identical overall yield (28%), by treatment of the crude tosyl compound (syrup) with sodium methoxide; in this case it was isolated by sublimation at 120—140° (bath)/10 mm.

1 : 3-2 : 4-*Diethylidene* 6-*Allyl Sorbitol*.—1 : 3-2 : 4-Diethylidene 5 : 6-anhydrosorbitol (11·5 g.) was heated on the steam-bath for 6½ hours under reflux with a solution of sodium (1 g.) in allyl alcohol (50 c.c.). After addition of water (100 c.c.), the alkali was neutralised with carbon dioxide. Most of the allyl alcohol was removed by distillation under reduced pressure, and after the addition of sodium chloride the solution was extracted 7 times with ether (total 200 c.c.). The extracts were dried (K_2CO_3) and the solvent was removed. Distillation of the very viscous oil gave 1 : 3-2 : 4-*diethylidene* 6-*allyl sorbitol* (10·2 g., 55%), b. p. 115—130° (bath)/0·0001 mm., n_D^{25} 1·4780, $[\alpha]_D^{25}$ −1·3° (*c*, 3 in ethanol) (Found: C, 56·7; H, 8·35. $C_{12}H_{20}O_6$ requires C, 56·9; H, 8·1%).

Penta-acetyl 6-*Allyl Sorbitol*.—6-Allyl 1 : 3-2 : 4-diethylidene sorbitol (10·2 g.) was heated with 4% sulphuric acid (100 c.c.) and ethanol (25 c.c.) on the steam-bath for 5 hours, the liberated acetaldehyde being allowed to escape. The solution was extracted once with ether to remove oily impurities, and then neutralised with barium carbonate (20 g.). The barium salts were removed, and the aqueous solution was evaporated under reduced pressure. The syrup was dried by several evaporations with small amounts of ethanol, and was then dissolved in ethanol (20 c.c.), filtered from a small quantity of insoluble matter, evaporated, and finally dried over phosphoric oxide under reduced pressure. This 6-allyl sorbitol (8·35 g.) failed to crystallise, and it was therefore heated with acetic anhydride (42 c.c.) and fused sodium acetate (4·2 g.) on the steam-bath for 8 hours. Excess of anhydride was removed by distillation under reduced pressure, and the residue was stirred with water for 1½ hours. The product was an oil (14·9 g., 92%) which failed to crystallise, and was distilled. *Penta-acetyl* 6-*allyl sorbitol* had b. p. 140° (bath)/0·0001 mm., n_D^{25} 1·4548, $[\alpha]_D^{25}$ +0·86° (*c*, 2·7 in chloroform) (Found: C, 52·1; H, 6·8; Ac, 48·4. $C_{18}H_{26}O_{11}$ requires C, 52·8; H, 6·5; Ac, 49·4%).

Penta-acetyl 6-(2 : 3-*Dibromopropyl*) *Sorbitol*.—A solution of penta-acetyl 6-allyl sorbitol (13·9 g.) in carbon tetrachloride (60 c.c.) was stirred vigorously and cooled whilst a solution of bromine (5·4 g.) in carbon tetrachloride (20 c.c.) was added during 4 hours, the temperature being kept at −6° to −8°. Stirring was continued for 15 minutes after all the bromine had been added. The carbon tetrachloride solution was washed with sodium hydrogen carbonate solution (50 c.c.), containing sodium thiosulphate (0·5 g.), and dried (Na_2SO_4). The solvent was removed by distillation, and the syrup evaporated several times with methanol, and finally heated at 80°/0·0001 mm. for an hour; yield of *dibromide*, 17·6 g. (93%) (Found: Br, 27·2. $C_{18}H_{24}O_{11}Br_2$ requires Br, 27·0%).

Hepta-acetyl 6-(2 : 3-*Dimercaptopropyl*) *Sorbitol*.—The above dibromide (17 g.), potassium thiolacetate (8 g.), ethanol (60 c.c.), and thiolacetic acid (0·2 c.c.) were heated together on the steam-bath in a 3-necked flask, fitted with reflux condenser, mercury-sealed stirrer, and nitrogen-inlet tube. Vigorous stirring was necessary to prevent violent bumping (caused by precipitated potassium bromide). A slow stream of dry nitrogen was passed through the apparatus during the reaction (6 hours); the deep-yellow solution was then treated with water (300 c.c.), and the insoluble oil was isolated by extraction with ether. The dried (Na_2SO_4) extracts were evaporated in a stream of nitrogen, and the residual syrup was heated to constant weight at 70°/0·0001 mm., to give *hepta-acetyl* 6-(2 : 3-*dimercaptopropyl*) *sorbitol* (16·1 g., 97%) (Found: S, 11·2. $C_{20}H_{30}O_{12}S_2$ requires S, 11·0%). Light absorption: max. 2280 A.; ε = 7800.

Deacetylation. A solution of the hepta-acetate (15·6 g.) in dry methanol (150 c.c.) was cooled to *ca.* −20° and vigorously stirred during addition of methanolic barium methoxide (62 c.c.; 1·04N.), air being excluded by a slow stream of dry nitrogen. After 25 minutes, a fine yellow precipitate suddenly appeared, and after a further 40 minutes it was filtered off in an atmosphere of nitrogen, washed well with methanol and with dry ether, and dried under reduced pressure, first over calcium chloride and finally over phosphoric oxide. The crude barium salt of 6-(2 : 3-dimercaptopropyl) sorbitol (8·4 g.) had $[\alpha]_D^{25}$ +3·15° (*c*, 5 in water) (Found: C, 32·0; H, 6·3; S, 11·2; thiol S, 10·7; Ba, 24·3. Calc. for $C_9H_{18}O_8S_2Ba$: C, 25·5; H, 4·3; S, 15·1; Ba, 32·4%). It formed a fine yellow deliquescent powder, easily soluble in water, and was used without further purification for pharmacological tests. The analytical figures suggest either tenacious retention of solvent or incomplete deacetylation; a triacetate, $C_{15}H_{24}O_8S_2Ba$, requires C, 32·7; H, 4·4; S, 11·7; Ba, 25·0%. The high thiol value, compared with the total sulphur content, indicates almost complete deacetylation of the acetylthio-groups, however.

1 : 2-3 : 4-*Diisopropylidene* 5 : 6-*Anhydromannitol*.—1 : 2-3 : 4-Diisopropylidene mannitol (Wiggins, *J.*, 1946, 13) (50 g.) was dissolved in dry pyridine (100 c.c.), and a solution of toluene-*p*-sulphonyl chloride (38 g.) in pyridine (70 c.c.) was added, with stirring, during 1 hour, the temperature being kept below 10° by ice-cooling. The mixture was set aside overnight and then concentrated under reduced pressure. Water and chloroform were added, and the chloroform layer was removed and washed successively with dilute hydrochloric acid, water, and sodium hydrogen carbonate solution, and then dried (Na_2SO_4). This solution was cooled to 0° and gradually treated below 5° with a solution of sodium (4·5 g.) in dry methanol (80 c.c.); after a further 10 minutes at 5°, water was added to dissolve the precipitated sodium toluene-*p*-sulphonate, the chloroform layer was removed, and the aqueous portion was extracted once more with chloroform. The combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated to a syrup. Distillation then furnished 1 : 2-3 : 4-diisopropylidene 5 : 6-anhydromannitol (27 g., 63%), b. p. 98°/0·003 mm., n_D^{20} 1·4500.

6-*Allyl* 1 : 2-3 : 4-*Diisopropylidene Mannitol*.—A solution of the anhydro-compound (25 g.) in allyl alcohol (100 c.c.) containing sodium (4 g.) was boiled under reflux for 6 hours and then concentrated to small bulk. After dilution with water, and neutralisation with hydrochloric acid, the lower oily layer was taken up in chloroform, and the aqueous portion was extracted twice with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to an oil, which on distillation gave **6-*allyl* 1 : 2-3 : 4-*diisopropylidene mannitol*** (28 g., 90%), b. p. 140—142°/0·003 mm., n_D^{25} 1·4570 (Found: C, 59·9; H, 8·7. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·7%).

1-*Allyl Mannitol*.—6-Allyl 1 : 2-3 : 4-diisopropylidene mannitol (26 g.), suspended in N-sulphuric acid (50 c.c.), was heated on the steam-bath for 4 hours (the solution became homogeneous after ½ hour). The cooled solution was neutralised with barium carbonate, filtered, and evaporated to a solid residue (18 g., 94%) of **1-*allyl mannitol***, which could be crystallised in small quantities from ethanol in the form of plates, m. p. 99—101°, $[\alpha]_D^{25}$ +18° (*c*, 1 in water) (Found: C, 48·0; H, 8·3. $C_9H_{18}O_6$ requires C, 48·6; H, 8·2%). When heated in ethanol for several minutes it appeared to undergo polymerisation, a flocculent precipitate being slowly formed.

Penta-acetyl* 1-*Allyl Mannitol*.**—1-Allyl mannitol (17 g.) was heated on the steam-bath for 2 hours with acetic anhydride (70 c.c.) and fused sodium acetate (10 g.). The solution was concentrated under reduced pressure and then stirred with water to decompose any remaining anhydride. The oil was taken up in chloroform, and the aqueous solution was extracted once more with chloroform. The combined extracts were washed with water, and with sodium hydrogen carbonate solution, and were then dried (Na_2SO_4) and evaporated to an oil (31 g., 94%), which slowly crystallised. Recrystallisation from methanol gave needles of ***penta-acetyl* 1-*allyl mannitol, m. p. 63—64°, $[\alpha]_D^{17}$ +30° (*c*, 2·3 in chloroform) (Found: C, 52·4; H, 6·7. $C_{19}H_{28}O_{11}$ requires C, 52·7; H, 6·5%).

Penta-acetyl* 1-(2 : 3-*Dibromopropyl*) *Mannitol*.**—The above penta-acetate (30·2 g.) was dissolved in carbon tetrachloride (100 c.c.) and treated at 0° with bromine (11 g.), added slowly during 1½ hours with stirring. Chloroform (20 c.c.) was then added to dissolve a small amount of oil which had separated, and the solution was washed with sodium hydrogen carbonate solution and then with sodium hydrogen sulphite solution, and finally dried (Na_2SO_4) and evaporated to a pale yellow syrup (41 g., 99%), which consisted essentially of ***penta-acetyl* 1-(2 : 3-*dibromopropyl*) *mannitol (Found: Br, 26·6. $C_{19}H_{28}O_{11}Br_2$ requires Br, 27·0%).

***Hepta-acetyl* 1-(2 : 3-*Dimercaptopropyl*) *Mannitol*.**—The dibromide (41 g.) and potassium thiolacetate (19 g.) in ethanol (200 c.c.) were heated under reflux for 6 hours and then set aside overnight. Water (600 c.c.) was added, most of the alcohol was removed by distillation under reduced pressure, and the product was extracted with ether. The dried ($CaCl_2$) extracts were evaporated to a brown syrup of the ***hepta-acetyl* compound** (40·5 g., 100%) (Found: S, 10·5. $C_{21}H_{32}O_{13}S_2$ requires S, 11·0%).

***Deacetylation*.** The hepta-acetate (20 g.) in dry methanol (55 c.c.) was treated, as previously described, with 1·13N-barium methoxide (80 c.c.) and gave a crude barium salt (15 g.) (Found: S, 11·2; thiol S, 9·5. Calc. for $C_9H_{14}O_8S_2Ba$: S, 15·1%).

***Direct Allylation of* 1 : 2-3 : 4-*Diisopropylidene Mannitol*.**—1 : 2-3 : 4-Diisopropylidene mannitol (7 g.) in acetone (40 c.c.), sodium hydroxide (10 g.), and water (15 c.c.) was treated at 70° with allyl bromide (4·6 g.) in acetone (10 c.c.) under conditions similar to those described above for 1 : 3-2 : 4-diethylidene sorbitol. The product, isolated by ether-extraction, was distilled, and gave an oil (5·3 g.), b. p. 160°/0·007 mm., n_D^{25} 1·4570, $[\alpha]_D^{25}$ +14·2° (*c*, 5 in chloroform), which was a mixture of mono- and di-allyl compounds (Found: C, 60·8; H, 9·6. Calc. for $C_{15}H_{26}O_6$: C, 59·6; H, 8·7. Calc. for $C_{18}H_{30}O_6$: C, 63·2; H, 7·0%).

This mixture (5 g.) was hydrolysed by being heated with 3% aqueous sulphuric acid for 1½ hours, a little alcohol being added to effect dissolution. The cooled solution was extracted once with ether to remove oily impurities, and the acid was neutralised with barium carbonate (4 g.). The barium salts were removed by filtration, and the aqueous solution was evaporated under reduced pressure from a water-bath at 75°. The syrup was taken up in hot ethanol and filtered. Evaporation of the solvent, and addition of ethyl acetate to the residue, gave a solid (2·6 g.), m. p. 50—80°, which on recrystallisation from acetone, and ethanol–ethyl acetate, gave 1'-allyl mannitol, m. p. 98—101°, $[\alpha]_D^{25}$ +17·6° (*c*, 0·8 in water), identical with that prepared *via* the 5 : 6-anhydro-compound.

Evaporation of the mother-liquors gave a syrup (2·6 g.), which was acetylated by being heated on the steam-bath with acetic anhydride (10 c.c.) and fused sodium acetate (2 g.) for 4 hours. Excess of anhydride was decomposed by stirring the mixture with water (100 c.c.) for 2 hours, and the acetyl derivative was isolated by 3 extractions with chloroform. The extracts were washed with sodium hydrogen carbonate solution, the washings being extracted twice with fresh chloroform. The dried (Na_2SO_4) extracts were evaporated, and the residue was distilled to give a colourless syrup (4·1 g.), b. p. 140°/0·0001 mm., n_D^{25} 1·4534, $[\alpha]_D^{25}$ +24·4° (*c*, 4 in chloroform) (Found: Ac, 43·8; equiv., from unsaturation value with ICl, 158. Calc. for monoallyl penta-acetate, $C_{19}H_{28}O_{11}$: Ac, 49·8; equiv., 216. Calc. for diallyl tetra-acetate, $C_{18}H_{26}O_{10}$: Ac, 40·0%; equiv., 107·5). After one month, the syrup deposited crystals (0·6 g.), m. p. 39—54°, which were drained on porous tile. Six recrystallisations from light petroleum (b. p. 60—80°) gave ***penta-acetyl* 2-*allyl mannitol***, m. p. 78—79°, $[\alpha]_D^{25}$ +18·2° (*c*, 1 in chloroform) (Found: C, 52·9; H, 6·4. $C_{19}H_{28}O_{11}$ requires C, 52·8; H, 6·5%). The material depressed the m. p. of penta-acetyl 1-allyl mannitol (m. p. 63—64°) to 54—55°.

Allylation of* 1 : 2-5 : 6-*Diisopropylidene Mannitol*.**—1 : 2-5 : 6-Diisopropylidene mannitol (Baer, *loc. cit.*) (22·6 g., 0·09 mol.) in water (20 c.c.) and acetone (85 c.c.) was treated with sodium hydroxide solution (32 g. of NaOH in 32 c.c. of water). The mixture, which formed two layers, was vigorously stirred and heated in a water-bath at 75° during addition (4 hours) of a solution of allyl bromide (15·1 g., 0·125 mol.) in acetone (20 c.c.). After working up in the usual way, ether extraction gave an oil, which on distillation furnished **3-*allyl* 1 : 2-5 : 6-*diisopropylidene mannitol (23 g., 87%), b. p. 139°/0·001 mm., n_D^{25} 1·4562, $[\alpha]_D^{25}$ +5·3° (*c*, 1·0 in chloroform) (Found: C, 59·9; H, 8·7. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·7%).

3-*Allyl Mannitol*.—3-Allyl 1 : 2-5 : 6-diisopropylidene mannitol (23 g.) was heated with 6% aqueous sulphuric acid (100 c.c.) on the steam-bath for 4 hours. The solution was cooled, and extracted once with ether to remove oily impurities, and then neutralised with barium carbonate (40 g.) and filtered;

the residue was well washed with hot water. The aqueous solution was evaporated under reduced pressure from a water-bath at 75°, and the residue so obtained was dried by evaporation several times with ethanol. The semi-solid product (16 g.) was dissolved in hot ethanol and filtered from a small amount of insoluble material. Evaporation of the alcoholic solution until crystals formed, and addition of ethyl acetate, gave 3-allyl mannitol (10 g., 59%), m. p. 112—114°; when recrystallised from ethanol–ethyl acetate it formed hard rosettes, m. p. 117°, $[\alpha]_D^{20}$ +15·3° (*c*, 1·0 in water) (Found: C, 48·3; H, 8·2. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2%). Wrigley and Yanovsky (*loc. cit.*) give m. p. 119—120° (corr.), $[\alpha]_D^{20}$ +15·6° (*c*, 4 in water). Evaporation of the mother-liquors gave a syrup (4·5 g.).

Penta-acetyl 3-*Allyl Mannitol*.—3-Allyl mannitol (9·5 g.), acetic anhydride (38 c.c.), and fused sodium acetate (4·25 g.) were heated together on the steam-bath for 2½ hours. Most of the excess anhydride was removed by distillation under reduced pressure, and the residue was stirred with water for 30 minutes. The insoluble syrup was taken up in chloroform (5 × 50 c.c.), and the extracts were washed with sodium hydrogen carbonate solution, the washings being extracted twice more with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield *penta-acetyl* 3-*allyl mannitol* (18·4 g., 100%), which distilled as a colourless oil, b. p. 120—150° (bath)/0·001 mm., n_D^{20} 1·4532, $[\alpha]_D^{20}$ +33·3° (*c*, 3 in chloroform) (Found: C, 52·4; H, 6·4; Ac, 51·0; equiv., by ICl titration, 214. $C_{19}H_{28}O_{11}$ requires C, 52·8; H, 6·5; Ac, 49·4; equiv., 216).

Penta-acetyl 3-(2 : 3-*Dibromopropyl*) *Mannitol*.—A solution of penta-acetyl 3-allyl mannitol (2·2 g.) in carbon tetrachloride (15 c.c.) was treated with bromine (0·85 g.) in carbon tetrachloride (15 c.c.), added with vigorous stirring during 2 hours, the temperature being kept below 0°. The solution was then shaken with aqueous sodium thiosulphate, dried (Na_2SO_4), and evaporated, to yield *penta-acetyl* 3-(2 : 3-*dibromopropyl*) *mannitol* as a syrup (2·8 g., 94%), n_D^{20} 1·4794 (Found: Br, 27·4. $C_{19}H_{28}O_{11}Br_2$ requires Br, 27·0%).

Treatment of the dibromide with potassium thiolacetate in the usual way, followed by deacetylation of the liquid bisthiolacetate with barium methoxide, gave the crude barium salt of the dithiol as a pale yellow powder, readily soluble in water. The analysis was typical of this type of compound (Found: S, 11·5; thiol S, 10·1; Ba, 28·1. Calc. for $C_9H_{14}O_4S_2Ba$: S, 15·15; Ba, 32·4%).

Allylation of 1 : 4-3 : 6-*Dianhydromannitol*.—(*a*) A mixture of 1 : 4-3 : 6-dianhydromannitol (Wiggins, *J.*, 1945, *5*; Bladon and Owen, preceding paper) (14·6 g., 0·1 mol.), acetone (100 c.c.), sodium hydroxide (36 g.), and water (70 c.c.) was treated at 60—70° with a solution of allyl bromide (15·1 g., 0·125 mol.) in acetone (30 c.c.) during 1½ hours with vigorous stirring. Heating and stirring were continued for a further 2 hours, and the product was then isolated as previously described, giving an oil (4·2 g.), b. p. 160°/10 mm., n_D^{20} 1·4850 (Found: equiv., by ICl titration, 54. Calc. for diallyl derivative, $C_{15}H_{24}O_4$: equiv., 56·5).

The aqueous solution from the ether-extraction was evaporated to dryness under reduced pressure, and the solid residue was extracted with chloroform (Soxhlet). Evaporation of the dried (Na_2SO_4) extracts gave unchanged 1 : 4-3 : 6-dianhydromannitol (9 g.), m. p. and mixed m. p. 83—85°, after recrystallisation from ethyl acetate.

(*b*) A mixture of 1 : 4-3 : 6-dianhydromannitol (29·2 g., 0·2 mol.), dioxan (100 c.c.), sodium hydroxide (72 g.), and water (92 c.c.) was similarly treated at 70° with allyl bromide (30 g., 0·25 mol.) in dioxan (30 c.c.), and gave a product (14·5 g.), b. p. 145°/10 mm., n_D^{20} 1·4802, $[\alpha]_D^{20}$ +157° (*c*, 2 in chloroform), which also consisted largely of 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol (Found: C, 62·6; H, 8·2; equiv., by ICl titration, 59·6. Calc. for $C_{15}H_{24}O_4$: C, 63·7; H, 8·0%; equiv., 56·5). Gregory and Wiggins (*J.*, 1947, 1405) give b. p. 173°/10 mm., n_D^{21} 1·4847, $[\alpha]_D^{20}$ +160° (*c*, 1·5 in chloroform).

(*c*) Sodium (4·6 g., 0·2 atom), in small pieces, was added to a solution of 1 : 4-3 : 6-dianhydromannitol (29·2 g., 0·2 mol.) in liquid ammonia (500 c.c.) contained in a 1-l. flask. The sodium dissolved with evolution of hydrogen. After 1 hour, the small amount of undissolved sodium was removed, the ammonia was boiled off on the steam-bath, and the residual solid was heated under reduced pressure to remove the last traces of ammonia. The fine white powder was transferred to a 500-c.c. flask, fitted with a mercury-sealed stirrer and reflux condenser, and was heated on the steam-bath with dry benzene (100 c.c.) and allyl bromide (50 g.) for 22 hours, with stirring, a further 25 g. of allyl bromide being added after 12 hours. The reaction mixture was treated with water (200 c.c.), the benzene layer was separated, and the aqueous solution was acidified with hydrochloric acid and continuously extracted with ether for 12 hours. The benzene and the ether extracts were dried (Na_2SO_4) and evaporated, yielding oils weighing, respectively, 10·75 g. and 13·1 g. Distillation of the combined oils gave a main fraction (20·5 g.), b. p. 107—115°/1 mm., n_D^{20} 1·4901 (Found: equiv., by ICl titration, 77; corresponding to a mixture containing *ca.* 45% of monoallyl derivative).

This mixture (20 g.) was heated under reflux with phthalic anhydride (16·8 g.) and dry pyridine (50 c.c.) for 23 hours. The excess of pyridine was removed by distillation under reduced pressure, and the residue was taken up in chloroform (100 c.c.) and washed successively with 2*N*-hydrochloric acid, water, 2*N*-sodium carbonate, and water. The chloroform solution was dried (Na_2SO_4) and evaporated to a mobile liquid (7·1 g.), which on distillation gave 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol (6·3 g.), b. p. 87—89°/0·05 mm., n_D^{20} 1·4842, $[\alpha]_D^{20}$ +160° (*c*, 1·7 in chloroform), $[\alpha]_D^{20}$ +141° (*c*, 5·7 in chloroform) (Found: C, 63·6; H, 8·0; equiv., by ICl titration, 57·4. Calc. for $C_{15}H_{24}O_4$: C, 63·7; H, 8·0%; equiv., 56·5).

The acid washings of the chloroform solution were discarded. The sodium carbonate extracts and the final water-washing were acidified to Congo-red with hydrochloric acid and extracted 4 times with chloroform (100-c.c. portions). The extracts were washed once with water, dried (Na_2SO_4), and evaporated to a very viscous syrup (23·1 g.), which solidified on being stirred with ether. The solid (16·9 g.), m. p. 105—110°, was filtered off, and a portion was recrystallised 4 times from ethyl acetate (with charcoal) to give hard prisms of 2-*allyl* 1 : 4-3 : 6-*dianhydromannitol* 5-(*hydrogen phthalate*), m. p. 110°, $[\alpha]_D^{20}$ +80° (*c*, 0·9 in chloroform) (Found: C, 61·05; H, 5·7. $C_{17}H_{18}O_7$ requires C, 61·05; H, 5·4%). The rotation in 2*N*-sodium hydroxide, $[\alpha]_D^{20}$ +92° (*c*, 0·8), was unchanged after 12 hours at room temperature, showing that the ester was not appreciably hydrolysed under these conditions.

2-*Allyl* 1 : 4-3 : 6-*Dianhydromannitol*.—The foregoing hydrogen phthalate (16·8 g.) was boiled under reflux with sodium hydroxide (6·5 g.) in water (10 c.c.) for 2 hours, and then heated for a further 6 hours

on the steam-bath. The solution, diluted with water (50 c.c.) and treated with sodium hydrogen carbonate (4 g.), was exhaustively extracted with ether (12 hours). The dried (Na_2SO_4) extracts yielded, on evaporation, an oil (9·3 g.), which on distillation furnished *2-allyl* **1 : 4-3 : 6-***dianhydromannitol* (8·1 g., 86%) as a colourless mobile liquid, b. p. 85°/0·01 mm., n_D^{18} 1·4920, $[\alpha]_D^{18}$ +113° (*c*, 2·2 in chloroform) (Found: C, 58·0; H, 7·7; equiv., by ICl titration, 93. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%; equiv., 93).

5-Acetyl 2-Allyl **1 : 4-3 : 6-***Dianhydromannitol*.—2-Allyl **1 : 4-3 : 6**-dianhydromannitol (8 g.), acetic anhydride (25 c.c.), and fused sodium acetate (2·5 g.) were heated together on the steam-bath overnight. The mixture was shaken with water (50 c.c.) until the excess of anhydride was destroyed, and the product was isolated by 4 extractions with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, to give an oil (9·3 g.) which on distillation yielded *5-acetyl 2-allyl* **1 : 4-3 : 6-***dianhydromannitol* as a colourless mobile liquid (7·7 g., 82%), b. p. 92—93°/0·01 mm., n_D^{18} 1·4769, $[\alpha]_D^{18}$ +185·6° (*c*, 2·5 in chloroform) (Found: C, 58·1; H, 6·9; equiv., by ICl titration, 114·5. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%; equiv., 114).

5-Acetyl 2-(2 : 3-Dibromopropyl) **1 : 4-3 : 6-***Dianhydromannitol*.—5-Acetyl 2-allyl **1 : 4-3 : 6**-dianhydromannitol (7·4 g.) in carbon tetrachloride (80 c.c.) was treated with bromine (6 g.) in the same solvent (30 c.c.), added with cooling and stirring during ½ hour, the temperature being kept below −20°. The solution was allowed to warm to room temperature and was diluted with chloroform (40 c.c.) and stirred for a further 20 minutes in order to dissolve some viscid material which had separated. The solution was then washed with sodium hydrogen carbonate solution (50 c.c.) containing sodium thiosulphate (1 g.), then dried (Na_2SO_4) and evaporated. The viscous syrup (11·6 g., 92%) on distillation from a wide-necked retort gave *5-acetyl 2-(2 : 3-dibromopropyl)* **1 : 4-3 : 6-***dianhydromannitol* (9·3 g.), b. p. 120—170° (air-bath)/0·0001 mm., n_D^{18} 1·5241, $[\alpha]_D^{18}$ +116° (*c*, 2·3 in chloroform) (Found: C, 34·1; H, 4·4; Br, 40·9. $C_{11}H_{14}O_5Br_2$ requires C, 34·0; H, 4·2; Br, 41·2%).

Triacetyl 2-(2 : 3-Dimercaptopropyl) **1 : 4-3 : 6-***Dianhydromannitol*.—The above 5-acetyl compound (8·5 g.), potassium thiolacetate (6 g.), and ethanol (30 c.c.) were heated under reflux, with vigorous stirring, under nitrogen for 7 hours. The mixture was poured into water, and the product was isolated by 6 extractions with ether. The extracts were dried (Na_2SO_4) and evaporated, and the product on distillation gave *triacetyl 2-(2 : 3-dimercaptopropyl)* **1 : 4-3 : 6-***dianhydromannitol* (6·2 g.), b. p. 170—180° (air-bath)/0·0001 mm., n_D^{18} 1·5286, $[\alpha]_D^{18}$ +133° (*c*, 2·0 in chloroform) (Found: C, 46·8; H, 5·7; S, 16·7. $C_{18}H_{28}O_7S_2$ requires C, 47·6; H, 5·9; S, 17·0%). Light absorption: max. 2310 A., ε = 8300.

Deacetylation. The bisthiolacetate (5·2 g.) was heated under reflux with 2% methanolic hydrogen chloride (50 c.c.) for 4 hours under nitrogen. During this time, a brilliant purple colour appeared in the solution, reached a maximum intensity after 2 hours, and then faded, so that it had almost disappeared after 4 hours. The solvent was removed by distillation under reduced pressure and the residual syrup was kept for several hours over solid potassium hydroxide, under reduced pressure. On distillation from a retort, it gave, with slight decomposition, *2-(2 : 3-dimercaptopropyl)* **1 : 4-3 : 6-***dianhydromannitol* (2·9 g., 83%), as a yellow, viscous, cloudy liquid, b. p. 150° (air-bath)/0·0001 mm., n_D^{18} 1·5492, $[\alpha]_D^{18}$ +84° (*c*, 2·3 in chloroform) (Found: S, 22·7; thiol S, 21·4. $C_9H_{14}O_4S_2$ requires S, 25·4%). It was readily soluble in water.

Allylation of **1 : 4-3 : 6-***Dianhydrosorbitol*.—(*a*) Under conditions similar to those used for the direct allylation of **1 : 4-3 : 6**-dianhydromannitol in acetone solution, **1 : 4-3 : 6**-dianhydrosorbitol (14·6 g.) and allyl bromide (15·1 g.) gave an oil (2·1 g.), b. p. 90°/0·1 mm., n_D^{18} 1·4818 (Found: equiv., by ICl titration, 58), consisting mainly of diallyl derivative. Unchanged dianhydrosorbitol (7 g.) was recovered.

(*b*) **1 : 4-3 : 6**-Dianhydrosorbitol (14·6 g., 0·1 mol.) was converted into the sodium derivative by reaction with sodium (2·3 g., 0·1 atom) in liquid ammonia. The dried salt was then treated with allyl bromide (25 g.) in boiling benzene (50 c.c.) as previously described, and the product (9·3 g.), on distillation, gave a mixture of the mono- and di-allyl derivatives, b. p. 100°/0·5 mm., n_D^{18} 1·4850 (Found: equiv., by ICl titration, 72), which was heated with phthalic anhydride (7·15 g.) in dry pyridine (20 c.c.) as before. There were obtained **2 : 5-diallyl 1 : 4-3 : 6-**dianhydrosorbitol (3·6 g.), b. p. 90°/0·1 mm., n_D^{17} 1·4804, $[\alpha]_D^{18}$ +99° (*c*, 4·8 in chloroform) (Found: C, 63·8; H, 7·9; equiv., by ICl titration, 57. Calc. for $C_{12}H_{18}O_4$: C, 63·7; H, 8·0%; equiv., 56·5), and allyl **1 : 4-3 : 6**-dianhydrosorbitol hydrogen phthalate, a dark brown glass (probably a mixture of isomers) (9·3 g.) which failed to yield any crystalline salts (Found: equiv., by alkali titration, 313·5. Calc. for $C_{17}H_{18}O_7$: equiv., 334). Gregory and Wiggins (*loc. cit.*) for **2 : 5-diallyl 1 : 4-3 : 6-**dianhydrosorbitol give b. p. 185°/40 mm., n_D^{18} 1·4812, $[\alpha]_D^{18}$ +93·4° (*c*, 1·8 in chloroform).

The allyl **1 : 4-3 : 6**-dianhydrosorbitol hydrogen phthalate (8·7 g.) was boiled under reflux with a solution of sodium hydroxide (2·7 g.) in water (11 c.c.) for 2 hours. The mixture was then diluted with water (30 c.c.), sodium hydrogen carbonate (2 g.) was added, and the liquid was continuously extracted with ether for 40 hours. The extracts were dried (Na_2SO_4) and evaporated to an oil (3·35 g., 70%), which was distilled, and gave allyl **1 : 4-3 : 6**-dianhydrosorbitol as a colourless mobile liquid, b. p. 87—90°/0·05 mm., n_D^{18} 1·4891, $[\alpha]_D^{18}$ +15·1° (*c*, 2·5 in chloroform) (Found: C, 58·1; H, 7·75; equiv., by ICl titration, 97. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%; equiv., 93·1).

On acetylation, by the method previously described, using acetic anhydride and sodium acetate, it gave acetyl allyl **1 : 4-3 : 6**-dianhydrosorbitol, b. p. 160°/6 mm., n_D^{18} 1·4730, $[\alpha]_D^{18}$ +115° (*c*, 2 in chloroform) (Found: C, 57·65; H, 7·0. Calc. for $C_{11}H_{16}O_5$: C, 57·9; H, 7·1%).

These substances were probably mixtures of the 2- and the 5-allyl compound.

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Imperial College of Science and Technology,
S. Kensington, London, S.W.7.

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113. *Dithiols. Part VII. 5 : 6-Sorbitoleen and 1 : 2-Mannitoleen as Intermediates for the Preparation of Dithiols.**

By Peter Bladon and L. N. Owen.

By the action of sodium iodide, in acetone solution, on 5 : 6-ditosyl or 5 : 6-*dimethanesulphonyl* 1 : 3-2 : 4-*diethylidene sorbitol*, 1 : 3-2 : 4-*diethylidene* 5 : 6-*sorbitoleen* is obtained (cf. Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73); similarly 5 : 6-*dimethanesulphonyl* 1 : 2-3 : 4-*diisopropylidene mannitol* gives 1 : 2-3 : 4-*diisopropylidene* 5 : 6-*mannitoleen*. Removal of the protecting groups by acid hydrolysis then yields 5 : 6-*sorbitoleen* and 1 : 2-mannitoleen. Acetylation, followed by addition of bromine and reaction of the *dibromides* with potassium thiolacetate, gives the hexa-acetyl 5 : 6-dithiohexitols as mixtures of stereoisomers.

Addition of hypobromous acid to the tetra-acetates of 5 : 6-sorbitoleen and 1 : 2-mannitoleen, followed by reaction with sodium acetate, gives hexa-acetyl L-iditol and hexa-acetyl D-sorbitol respectively, and thus provides a new method for the interconversion of hexitols.

Experiments directed towards the synthesis of hydroxy-dithiols of the general formula $HO{\cdot}CH_2{\cdot}[CH(OH)]_n{\cdot}CH(SH){\cdot}CH_2{\cdot}SH$ have been described where $n = 0$ (Stocken, *J.*, 1947, 592), and where $n = 1$ and 2 (Evans, Fraser, and Owen, *J.*, 1949, 248). For the synthesis of the corresponding compound where $n = 3$, an unsaturated alcohol $HO{\cdot}CH_2{\cdot}[CH(OH)]_3{\cdot}CH{:}CH_2$ was required, and our attention was therefore directed towards the preparation of the hexitol derivatives, 1 : 2-mannitoleen and 5 : 6-sorbitoleen.

It has been known for some time that there are exceptions to Oldham and Rutherford's rule (*J. Amer. Chem. Soc.*, 1932, **54**, 366) in that secondary toluene-*p*-sulphonyl derivatives in the carbohydrate field will, in certain cases, react with sodium iodide in acetone solution. For example, both the tosyloxy-groups in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydromannitol (Hockett, Fletcher, Goepp, and Sheffield, *ibid.*, 1946, **68**, 930), and one in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydrosorbitol (*idem*, *ibid.*, p. 927) react with the reagent at 120° (see also Folkers *et al.*, *ibid.*, 1948, **70**, 2325; Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133). Of particular interest is the behaviour of vicinal tosyloxy-groups; Levene and Mehltretter (*Enzymologia*, 1937, **4**, ii, 232) found that when tritosyl glycerol was heated with sodium iodide in acetone all the groups were displaced, with the formation of an unsaturated compound, free iodine, and sodium toluene-*p*-sulphonate. Similar results were obtained by using tetratosyl erythritol (Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95), and in this case the unsaturated product was butadiene. More recently, Karrer, Schick, and Schwyzer (*Helv. Chim. Acta*, 1948, **31**, 784) have shown that the ditosyl derivatives of glyceraldehyde and of its acetal give acraldehyde.

In the hexitol series, a similar reaction was first observed by Hann, Ness, and Hudson (*loc. cit.*), who briefly reported that heating of 5 : 6-ditosyl 1 : 2-3 : 4-dibenzylidene sorbitol with sodium iodide in acetone at 100° resulted in precipitation of sodium toluene-*p*-sulphonate, liberation of iodine, and formation of 1 : 2-3 : 4-dibenzylidene 5 : 6-sorbitoleen. At the time of this publication, the exact nature of the linking of the benzylidene residues in the parent compound was uncertain, but in view of later work (Angyal and Lawler, *J. Amer. Chem. Soc.*, 1944, **66**, 837) the unsaturated compound must be formulated as 1 : 3-2 : 4-dibenzylidene 5 : 6-sorbitoleen (I).

The first stage in the reaction is undoubtedly the replacement of the primary tosyloxy-group by iodine. It is possible that the resulting intermediate product, containing a secondary tosyloxy-group and an iodine atom on adjacent carbon atoms, is unstable and breaks down directly to the unsaturated compound; more probably, however, the secondary tosyloxy-group in this intermediate undergoes replacement to form the vicinal di-iodide, a type of compound which is known to be unstable, and which then loses iodine in the usual way:

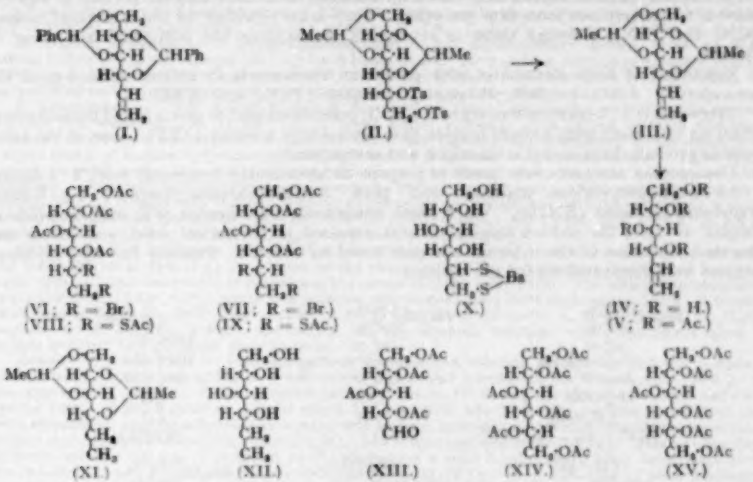
$$R{\cdot}CH(OTs){\cdot}CH_2{\cdot}OTs \longrightarrow R{\cdot}CH(OTs){\cdot}CH_2I \longrightarrow R{\cdot}CHI{\cdot}CH_2I \longrightarrow R{\cdot}CH{:}CH_2$$

In utilising this reaction for the preparation of 5 : 6-sorbitoleen, 1 : 3-2 : 4-diethylidene sorbitol was converted into 5 : 6-ditosyl 1 : 3-2 : 4-diethylidene sorbitol (II) (Wiggins, *J.*, 1946, 388; Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837), which reacted readily with sodium iodide in acetone at 100° and gave 1 : 3-2 : 4-*diethylidene* 5 : 6-*sorbitoleen* (III); the same product was also obtained from 5 : 6-*dimethanesulphonyl* 1 : 3-2 : 4-*diethylidene sorbitol* under the same conditions. Removal of the ethylidene residues from (III) by acid hydrolysis gave 5 : 6-*sorbitoleen* (IV) as a viscous liquid which could be distilled in high vacuum without decomposition; the overall yield from ditosyl diethylidene sorbitol was 70—80%. On

* A preliminary note on part of this work appeared in *Nature*, 1949, **163**, 140.

acetylation, with acetic anhydride and sodium acetate, it gave crystalline *tetra-acetyl* 5 : 6-*sorbitoleen* (V), which took up bromine in carbon tetrachloride solution and gave a *dibromide*, which partly crystallised.

The addition of bromine to (V) can theoretically give two products, (VI) and (VII), and the solid isomer must correspond to one of these formulæ, the other being present in the liquid portion. There is, however, no means of deciding which formula should be allocated to a particular isomer. The liquid and the crystalline substance were separately treated with potassium thiolacetate in boiling ethanol; both yielded syrups, but that derived from the crystalline dibromide slowly deposited a solid *hexa-acetyl* 5 : 6-*dithiohexitol*, (VIII) or (IX). In the reaction of the dibromides with potassium thiolacetate, partial epimerisation occurs on $C_{(5)}$; the solid product, therefore, does not necessarily possess the same (unknown) configuration as the crystalline dibromide. Deacetylation of the combined thiolacetate syrups with methanolic barium methoxide gave a crude barium salt of the 5 : 6-dithiohexitol (X).



Several other reactions were carried out on derivatives of 5 : 6-sorbitoleen. Hydrogenation of 1 : 3-2 : 4-diethylidene 5 : 6-sorbitoleen (III) over Raney nickel gave 1 : 3-2 : 4-*diethylidene* 5 : 6-*dideoxysorbitol* (XI), from which 5 : 6-*dideoxysorbitol* (XII) (*tetra-acetate*) was obtained by acid hydrolysis. Ozonolysis of tetra-acetyl 5 : 6-sorbitoleen (V) afforded a small yield of tetra-acetyl *aldehydo*-L-xylose (XIII) (cf. Major and Cook, *J. Amer. Chem. Soc.*, 1936, **58**, 2474; Wolfrom *et al.*, *ibid.*, 1931, **53**, 4379; 1944, **66**, 204). It was also possible to convert (V) into hexa-acetyl L-iditol; reaction of the unsaturated compound with *N*-bromosuccinimide in water and ether (a convenient source of hypobromous acid; see Raphael, *J.*, 1949, S 44) gave a non-crystalline bromohydrin of uncertain structure, and probably consisting of a mixture of isomers. This, on being heated with sodium acetate in acetic anhydride and acetic acid, gave a syrup from which hexa-acetyl L-iditol (XIV) was obtained in crystalline form; the yield was low, but no evidence was found of the presence of hexa-acetyl sorbitol (XV), the other possible product. Hexa-acetyl L-iditol was also obtained by treatment of the crystalline tetra-acetyl sorbitoleen dibromide, (VI) or (VII), with potassium acetate; this, however, does not prove the configuration of the original dibromide.

For the preparation of 1 : 2-mannitoleen and its derivatives the starting material was 1 : 2-3 : 4-diisopropylidene mannitol (Wiggins, *J.*, 1946, 13). Treatment with methanesulphonyl chloride in pyridine gave crystalline 5 : 6-*dimethanesulphonyl* 1 : 2-3 : 4-*diisopropylidene mannitol* (XVI); the corresponding 5 : 6-*ditosyl* compound was a liquid. When (XVI) was heated in acetone solution with sodium iodide, it gave 1 : 2-3 : 4-*diisopropylidene* 5 : 6-*mannitoleen* (XVII) as a mobile liquid. In the distillation of the crude reaction product,

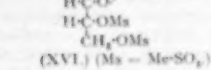
free iodine was liberated, indicating the presence of an iodine-containing compound, comparatively stable at moderate temperatures, but broken down when more strongly heated. Furthermore, from the non-volatile residue a small quantity of a water-soluble solid was obtained, which was identified as 1 : 2(or 5 : 6)-mannitoleen (XVIII). The mechanism of the formation of this compound, which involves the loss of the *iso*propylidene residues, is obscure; it appears that it must be produced during the distillation, since it is practically insoluble in chloroform and would not have been extracted from aqueous solution by this solvent during the working-up process. It was obtained in good yield from the di*iso*propylidene compound by acid hydrolysis, the overall yield from the dimethanesulphonyl derivative being 45%.

Acetylation of 1 : 2-mannitoleen gave the crystalline tetra-acetate, which reacted with bromine in carbon tetrachloride to give a solid dibromide, which was separated by fractional crystallisation into two *isomers*, m. p.s 111—112° and 76°. The optical rotations of these were almost identical, which suggested that they were polymorphic forms of the same substance, but a mixture of them melted over the range between their individual m. p.s and it was not possible to convert one form into the other. They must therefore be the structural isomers (XIX) and (XX), although there is no means of deciding the individual allocation of formulæ.

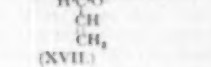
Treatment of both dibromides with potassium thiolacetate in boiling ethanol gave the hexa-acetyl 5 : 6-dithiohexitols, presumably mixtures of (XXI) and (XXII).

Tetra-acetyl 1 : 2-mannitoleen reacted with hypobromous acid to give a liquid bromohydrin, which on treatment with sodium acetate gave hexa-acetyl D-sorbitol (XV); none of the other possible product (hexa-acetyl D-mannitol) was encountered.

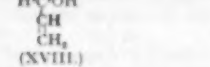
Unsuccessful attempts were made to prepare an unsaturated compound from 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol and from 3 : 4-*dimethanesulphonyl* 1 : 2-5 : 6-di*iso*-*propylidene mannitol* (XXIII). When these compounds were heated with sodium iodide in acetone at 110°, the sodium sulphonate was obtained in theoretical yield, and iodine was liberated, but none of the expected material could be isolated. Possibly the *iso*propylidene residues were eliminated during the reaction.



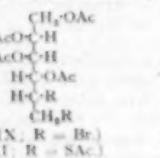
(XVI.) (Ms = Me·SO_2·)



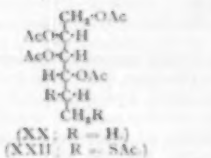
(XVII.)



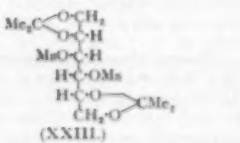
(XVIII.)



(XIX; R = Br.)
(XXI; R = SAc.)



(XX; R = H.)
(XXII; R = SAc.)



(XXIII.)

Since the completion of this work, Karrer and Davis (*Helv. Chim. Acta*, 1948, **31**, 1611) have reported experiments on the preparation of 1 : 2-mannitoleen from 1 : 2-3 : 4-di*iso*-propylidene mannitol by a method similar to that described above. Their results (with the ditosyl compound), however, differ in some respects from those obtained by us with the dimethanesulphonyl derivative. They found that treatment with sodium iodide in acetone gave 1 : 2-mannitoleen directly, and they failed to isolate the di*iso*propylidene compound, which was the main product in our experiments. Furthermore, the direct yield from the ditosyl di*iso*propylidene mannitol is only half of the overall yield obtained from the dimethanesulphonate.

Experimental.

5 : 6-*Ditosyl* 1 : 2-3 : 4-*Diethylidene Sorbitol*.—1 : 2-3 : 4-Diethylidene sorbitol (Bladon and Owen, preceding paper) (47 g.) in dry pyridine (250 c.c.) was treated with a solution of toluene-*p*-sulphonyl chloride (80 g., 2·1 mols.) in pyridine (160 c.c.) with cooling, and then set aside at room temperature for 21 hours. Addition of water (1500 c.c.) precipitated a solid, which was washed with water and with ethanol. This ditosyl derivative (45 g.), m. p. 169—170°, was sufficiently pure for most purposes;

further recrystallisation from acetone–ethanol raised the m. p. to 170—172°, $[\alpha]_D^{18}$ −12·0° (*c*, 1·7 in chloroform). Wiggins (*loc. cit.*) gives m. p. 173°, $[\alpha]_D$ −12·6°; Sullivan (*loc. cit.*) gives m. p. 172°, $[\alpha]_D^{20}$ −12·8°. It was obtained only as a by-product by these workers.

5 : 6-*Dimethanesulphonyl* 1 : 3-2 : 4-*Diethylidene Sorbitol*.—1 : 3-2 : 4-Diethylidene sorbitol (4·7 g.) was added slowly to a cooled solution of methanesulphonyl chloride (5·8 g.) in dry pyridine (12 c.c.). The mixture was set aside at 0° overnight and then diluted with water, which precipitated a viscid oil; a portion crystallised on trituration with methanol, and the main bulk was then seeded. The solid was well washed with water and recrystallised from methanol to give irregular prisms of the *dimethanesulphonate* (5·4 g.), m. p. 152—153°, $[\alpha]_D^{18}$ −5·2° (*c*, 1·0 in chloroform) (Found: C, 37·0; H, 6·3; S, 16·3. $C_{12}H_{22}O_{10}S_2$ requires C, 36·9; H, 5·7; S, 16·4%).

1 : 3-2 : 4-*Diethylidene* 5 : 6-*Sorbitoleen*.—(i) The ditosyl compound (41 g.), anhydrous sodium iodide (90 g.), and pure acetone (600 c.c.) were heated in a pressure bottle at 100° for 6 hours. The precipitated sodium toluene-*p*-sulphonate (29·5 g., 100%) was filtered off from the cooled reaction product, and well washed with cold acetone. The dark brown filtrate was evaporated to small bulk, and the residue was shaken with a solution of sodium thiosulphate (37·5 g.) in water (250 c.c.) to remove free iodine. The solution was then extracted with chloroform (4 × 50 c.c.); evaporation of the dried (Na_2SO_4) extracts gave a solid residue (15·4 g.), which on recrystallisation from ethyl acetate gave needles (10·9 g., 73%) of 1 : 3-2 : 4-*diethylidene* 5 : 6-*sorbitolen*, m. p. 120—122°, raised on further recrystallisation to 122—123°, $[\alpha]_D^{18}$ −23·8° (*c*, 1·1 in chloroform) (Found: C, 60·4; H, 7·9. $C_{10}H_{14}O_4$ requires C, 60·05; H, 8·1%).

(ii) Similar treatment of 5 : 6-dimethanesulphonyl 1 : 3-2 : 4-diethylidene sorbitol (1·95 g.) with sodium iodide (6·0 g.) in acetone (40 c.c.) for 6 hours at 100° gave sodium methanesulphonate (1·0 g., 100%), and, from the chloroform extracts, 1 : 3-2 : 4-diethylidene 5 : 6-sorbitoleen (1·0 g.), which on recrystallisation from ethyl acetate formed needles (0·6 g.), m. p. 122—124°.

5 : 6-*Sorbitolern*.—1 : 3-2 : 4-Diethylidene 5 : 6-sorbitoleen (15 g.) was heated with N-sulphuric acid (10 c.c.) and water (20 c.c.) at 100° for 11 hours under nitrogen. The cooled solution was then extracted once with ether to remove a small amount of oily impurity, and neutralised by the addition of a slight excess of barium hydroxide solution, followed by treatment with carbon dioxide. After being heated, to assist coagulation of the barium sulphate, it was filtered, the solid being well washed with hot water. Evaporation of the filtrate under reduced pressure gave a syrup, which was taken up in hot ethanol (50 c.c.), treated with charcoal, filtered, and evaporated to yield 5 : 6-*sorbitolern* (10·8 g.), a small portion of which was distilled at 100—130° (air-bath)/0·0001 mm.; n_D^{18} 1·5068, $[\alpha]_D^{18}$ +19·8° (*c*, 3·8 in water) (Found: C, 48·5; H, 8·3. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2%).

Tetra-acetyl 5 : 6-*Sorbitolern*.—5 : 6-Sorbitoleen (7·4 g.) was heated with acetic anhydride (40 c.c.) and fused sodium acetate (5 g.) for 9 hours on the steam-bath. The solution was then poured into cold water (400 c.c.) and well stirred to decompose the excess of acetic anhydride. The *tetra-acetate* separated as a white solid (12·5 g., 80%), which was collected and recrystallised from aqueous methanol; it formed small prisms, m. p. 57—58·5°, $[\alpha]_D^{18}$ −13·6° (*c*, 1·2 in chloroform) (Found: C, 52·8; H, 6·2. $C_{14}H_{20}O_8$ requires C, 53·15; H, 6·4%). Extraction of the aqueous solution with chloroform gave a further quantity (2·6 g.) of the same material.

Reaction of Tetra-acetyl 5 : 6-*Sorbitoleen with Bromine*.—A solution of bromine (9·8 g.) in carbon tetrachloride (40 c.c.) was added to a well-stirred and cooled solution of the tetra-acetate (15·8 g.) in the same solvent (150 c.c.), the temperature being kept at *ca.* 15° during the addition (2 hours) and for a further hour. A small quantity of solid which had separated was taken into solution by addition of a little chloroform, and the solution was washed with sodium hydrogen carbonate containing some sodium thiosulphate, and then with water, dried (Na_2SO_4), and evaporated to a syrup (25·7 g.). This was dissolved in warm ethanol (50 c.c.) and cooled to 0°, whereupon a solid crystallised. After being kept at 0° for 12 hours, it was collected and washed with ethanol (yield, 12·1 g.; m. p. 135—145°); recrystallisation from acetone gave small prisms of the *dibromide*, m. p. 152—154°, $[\alpha]_D^{18}$ −21·4° (*c*, 1·3 in chloroform) (Found: C, 35·5; H, 4·4; Br, 33·3. $C_{14}H_{20}O_8Br_2$ requires C, 35·3; H, 4·2; Br, 33·6%).

Evaporation of the ethanolic filtrate gave a syrup (10·4 g.), $[\alpha]_D^{18}$ +7·6° (*c*, 12 in chloroform), which contained the stereoisomeric dibromide (Found: Br, 32·0%).

Hexa-acetyl 5 : 6-*Dithiohexitol*.—(*a*) The crystalline dibromide (11·9 g.) and potassium thiolacetate (6·8 g.) were heated under reflux in ethanol (125 c.c.) for 7 hours. Water (250 c.c.) was then added, and the mixture was extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave a red syrup, which partly crystallised when kept for a week. The solid (3·5 g.; m. p. 86—87°) was freed from oil by trituration with cold methanol; recrystallisation from methanol then gave flat needles of the *hexa-acetyl* 5 : 6-*dithiohexitol*, m. p. 87—89°, $[\alpha]_D^{18}$ +49·4° (*c*, 2·8 in chloroform) (Found: C, 46·5; H, 5·9; S, 13·5. $C_{18}H_{26}O_{10}S_2$ requires C, 46·3; H, 5·6; S, 13·7%). Light absorption: max. 2300 A., ε = 7900.

(*b*) The liquid dibromide (9·8 g.), potassium thiolacetate (5·7 g.), thiolacetic acid (0·3 c.c.), and ethanol (40 c.c.) were heated under reflux for 6 hours. The product, isolated as described above, failed to crystallise, and was distilled, to yield the hexa-acetyl dithiohexitol (7·8 g.), b. p. 140—160°/0·001 mm., n_D^{18} 1·4895, $[\alpha]_D^{18}$ −17·8° (*c*, 1·5 in chloroform) (Found: C, 47·4; H, 5·8; S, 13·65%). Light absorption: max. 2290 A., ε = 5000.

Deacetylation. The syrupy hexa-acetate (21·3 g.) was dissolved in methanol (250 c.c.) and treated at −20° with 1·07*N*-methanolic barium methoxide (103 c.c.), air being excluded. The temperature was then allowed to rise to 0°, and stirring continued for a further 45 minutes. The precipitated barium salt was collected, washed with methanol and with ether, and dried under reduced pressure over calcium chloride and finally over phosphoric oxide; yield, 9·3 g. (Found: C, 28·6; H, 5·4; S, 17·6; thiol S, 10·8; Ba, 26·4. $C_6H_{12}O_4S_2Ba$ requires C, 20·6; H, 3·5; S, 18·4; Ba, 39·3%). The analysis, as usual with these compounds, indicated considerable contamination with other products; earlier work has shown that the deacetylation of acetylated polyhydroxy-dithiols does not proceed smoothly (cf. Part III, *J.*, 1949, 248; Part VI, preceding paper).

1 : 3-2 : 4-*Diethylidene* 5 : 6-*Dideoxysorbitol*.—1 : 3-2 : 4-Diethylidene 5 : 6-sorbitoleen (3 g.) in ethyl acetate (35 c.c.) was hydrogenated at ordinary temperature and pressure over Raney nickel catalyst; the filtered solution was then evaporated to a solid residue (3 g.), m. p. 84—86°. Recrystallisation from

light petroleum (b. p. 60—80°) gave 1 : 3·2 : 4-*diethylidene* 5 : 6-*dideoxysorbitol*, m. p. 85—86°, $[\alpha]_D^{18}$ +7·8° (*c*, 1·7 in chloroform) (Found: C, 59·55; H, 8·6. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%).

5 : 6-*Dideoxysorbitol*.—The diethylidene compound (3 g.) was heated on the steam-bath for 7 hours under reflux with methanol (5 c.c.) and 0·45*N*-sulphuric acid (10 c.c.). The cooled solution was extracted once with ether to remove a trace of oil, and was heated and treated with a slight excess of barium hydroxide solution, the excess then being removed with carbon dioxide. The barium salts were removed by filtration, and well washed with hot water; evaporation of the filtrate under reduced pressure gave a syrup, which was dissolved in warm methanol, filtered, and again evaporated to give 5 : 6-*dideoxysorbitol* (2·2 g.). A small portion, distilled at 150—160°(bath)/0·0001 mm., had n_D^{18} 1·4825, $[\alpha]_D^{18}$ +5·7° (*c*, 2·0 in water) (Found: C, 47·5; H, 9·5. $C_6H_{14}O_4$ requires C, 48·0; H, 9·4%).

Acetylation of 5 : 6-dideoxysorbitol (1·7 g.) with acetic anhydride (15 c.c.) and sodium acetate (1 g.) at 100° for 12 hours, gave *tetra-acetyl* 5 : 6-*dideoxysorbitol* (3·7 g.), b. p. 100—120°/0·0001 mm., n_D^{18} 1·4415, $[\alpha]_D^{18}$ +6·3° (*c*, 2·6 in chloroform) (Found: C, 53·0; H, 7·3. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·2%).

Tetra-acetyl aldehydo-L-*Xylose*.—Tetra-acetyl 5 : 6-sorbitoleen (0·5 g.) in ethyl acetate (10 c.c.) was treated with a stream of ozonised oxygen at −30° until no more ozone was absorbed. The solution was then shaken with hydrogen, in the presence of Raney nickel (1·5 g.), until no more was absorbed and evaporated under reduced pressure to an oil, which crystallised on the addition of light petroleum (b. p. 40—60°). Recrystallisation from dry ether gave tetra-acetyl *aldehydo*-L-xylose, m. p. 85—87°, $[\alpha]_D^{18}$ +17·6° (*c*, 1·0 in chloroform), which restored the colour to Schiff's reagent. Major and Cook (*loc. cit.*) give m. p. 90—91°, $[\alpha]_D^{20}$ +22·5° (*c*, 2 in absolute chloroform) (cf. also Wolfrom *et al.*, *loc. cit.*).

Hexa-acetyl L-*Iditol*.—(*a*) A solution of tetra-acetyl sorbitoleen (0·53 g.) in ether (5 c.c.) was shaken with *N*-bromosuccinimide (0·35 g.) and water (15 c.c.) overnight. The ethereal layer was separated, the aqueous portion was extracted twice with ether, and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was heated on the steam-bath with acetic anhydride (1·5 c.c.), acetic acid (1·5 c.c.), and sodium acetate (0·5 g.) for 26 hours (a crystalline precipitate of sodium bromide began to appear after 6 hours) and then stirred with water. The solution was extracted thrice with chloroform, and the extracts were washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to a syrup (0·65 g.), which was dissolved in dry ether containing a little methanol and treated with light petroleum (b. p. 40—60°). Hexa-acetyl L-iditol (0·2 g.) was obtained, m. p. 118—120°, $[\alpha]_D^{18}$ −26·8° (*c*, 1·0 in chloroform). Hann and Hudson (*J. Amer. Chem. Soc.*, 1942, **64**, 925) give m. p. 121—122° (corr.), $[\alpha]_D^{17}$ −25·5° (chloroform); Meyer and Reichstein (*Helv. Chim. Acta*, 1946, **29**, 161) give m. p. 119·5—120·5°, $[\alpha]_D^{18}$ −26·1° ± 2° (*c*, 0·9 in chloroform). Evaporation of the mother-liquors gave a syrup, from which no more solid material could be obtained.

(*b*) The crystalline dibromide of tetra-acetyl 5 : 6-sorbitoleen (0·7 g.; m. p. 152—153°), fused potassium acetate (1·25 g.), acetic acid (7·5 c.c.), and acetic anhydride (2·5 c.c.) were heated on a sand-bath under reflux for 60 hours. The mixture gradually darkened, and a precipitate of potassium bromide slowly appeared. The cooled mixture was then poured into water (40 c.c.) and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to a syrup. This was dissolved in a little methanol and treated with ether and light petroleum (b. p. 40—60°), whereupon crystals (0·2 g.) gradually separated. Recrystallisation from methanol–ether gave hexa-acetyl L-iditol, m. p. (and mixed m. p. with that obtained by the first method) 118—120°, $[\alpha]_D^{17}$ −26·6° (*c*, 1·2 in chloroform).

5 : 6-*Dimethanesulphonyl* 1 : 2·3 : 4-*Diisopropylidene Mannitol*.—To a solution of 1 : 2·3 : 4-di*iso*propylidene mannitol (Wiggins, *J.*, 1946, 13) (7·6 g.) in dry pyridine (18 c.c.) was added a solution of methanesulphonyl chloride (8·6 g.) in pyridine (18 c.c.), the temperature being kept below 20°. The mixture was set aside at 0° for 12 hours and then poured into water (250 c.c.). The precipitated oil crystallised on nucleation with a sample which had been caused to solidify by trituration with methanol. The solid was collected and well washed with water. One recrystallisation from methanol gave 10·65 g., m. p. 117—118°. Further recrystallisation from the same solvent gave pure 5 : 6-*dimethanesulphonyl* 1 : 2·3 : 4-*diisopropylidene mannitol*, m. p. 118—120°, $[\alpha]_D^{18}$ +25·1° (*c*, 2·0 in chloroform) (Found: C, 39·95; H, 6·3; S, 15·3. $C_{11}H_{22}O_{10}S_2$ requires C, 40·2; H, 6·3; S, 15·3%).

5 : 6-*Ditosyl* 1 : 2·3 : 4-*Diisopropylidene Mannitol*.—Similar treatment of 1 : 2·3 : 4-diisopropylidene mannitol (1·3 g.) in pyridine (6 c.c.) with toluene-*p*-sulphonyl chloride (2·1 g.) gave an oil on addition of water to the reaction mixture. It was isolated by chloroform extraction; the extracts were washed with hydrochloric acid, sodium hydrogen carbonate solution, and with water, dried (Na_2SO_4), and evaporated to a viscous oil (2·2 g.). This crude *ditosyl* derivative had $[\alpha]_D^{18}$ +12·1° (*c*, 4 in chloroform) (Found: S, 10·6. $C_{24}H_{34}O_{10}S_2$ requires S, 11·2%).

1 : 2·3 : 4-*Diisopropylidene* 5 : 6-*Mannitoleen*.—5 : 6-Dimethanesulphonyl 1 : 2·3 : 4-di*iso*propylidene mannitol (14·4 g.), sodium iodide (42 g.), and acetone (280 c.c.) were heated in a pressure bottle at 100° for 6½ hours. The precipitated sodium methanesulphonate (11·1 g.) was filtered off and washed with acetone. The filtrate and washings were evaporated to small bulk, and the residue was stirred with a solution of sodium thiosulphate (20 g.) in water (200 c.c.) and extracted 5 times with chloroform (50-c.c. portions). The dried (Na_2SO_4) extracts were evaporated to an oil (7·6 g.) which was distilled, b. p. 40°/0·1 mm.; the distillate contained free iodine, and it was therefore dissolved in chloroform and washed with sodium thiosulphate solution. The recovered oil on distillation gave colourless 1 : 2·3 : 4-*diisopropylidene* 5 : 6-*mannitoleen* (5·2 g.), b. p. 41°/0·1 mm., n_D^{18} 1·4401, $[\alpha]_D^{18}$ −5·5° (*c*, 2·4 in chloroform) (Found: C, 63·4; H, 8·6. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%).

A higher-boiling fraction and the still residue from the first distillation were combined, and oily material and iodine were removed by extraction with chloroform. The crystalline residue, on recrystallisation from methanol saturated with light petroleum (b. p. 40—60°) gave 1 : 2-mannitoleen as short needles, m. p. 147—149°, $[\alpha]_D^{18}$ +30·9° (*c*, 1·0 in water) (Found: C, 48·6; H, 7·9. Calc. for $C_6H_{12}O_4$: C, 48·6; H, 8·2%).

Hydrolysis of 1 : 2·3 : 4-*Diisopropylidene* 5 : 6-*Mannitoleen*.—A solution of the di*iso*propylidene compound (5·0 g.) in 0·3*N*-sulphuric acid (15 c.c.) was heated on the steam-bath for 7 hours in a slow

stream of nitrogen. The solution was then cooled and extracted once with ether to remove oily impurities. The acid was neutralised by addition, to the hot solution, of barium hydroxide solution in slight excess, followed by carbon dioxide. The barium salts were filtered off and washed with water, and the filtrate and washings were evaporated under reduced pressure. The solid residue was dissolved in warm methanol (100 c.c.) and the solution was filtered and evaporated, the residue being dried by evaporation with benzene and ethanol. Recrystallisation from ethanol–ethyl acetate gave 1 : 2-mannitoleen (2·25 g.), m. p. 144—148°, raised on further recrystallisation to m. p. 147—148°, $[\alpha]_D^{20}$ +30·0° (*c*, 1·0 in water). Karrer and Davis (*loc. cit.*) give m. p. 148·5—149°, $[\alpha]_D^{20}$ +33·4° (in water).

Tetra-acetyl 1 : 2-*Mannitoleen*.—1 : 2-Mannitoleen (2·0 g.), acetic anhydride (10 c.c.), and fused sodium acetate (1·0 g.) were heated on the steam-bath for 12 hours. The reaction mixture was then poured into water and stirred to decompose excess of anhydride. The mixture was cooled to 0°, and the solid was collected (yield, 4·3 g.; m. p. 79—82°). Recrystallisation from methanol gave plates of the tetra-acetyl derivative, m. p. 80—81°, $[\alpha]_D^{20}$ +49·4° (*c*, 1·0 in chloroform) (Found: C, 53·1; H, 6·0. Calc. for $C_{14}H_{20}O_9$: C, 53·15; H, 6·4%). Karrer and Davis (*loc. cit.*) give m. p. 81·5°.

Reaction of Tetra-acetyl 1 : 2-*Mannitoleen with Bromine*.—A solution of bromine (1·8 g.) in carbon tetrachloride (30 c.c.) was added slowly to a solution of the tetra-acetate (3·15 g.) in carbon tetrachloride (50 c.c.), the temperature being kept below 20°. Stirring was then continued for two hours, and the solution was washed with sodium hydrogen carbonate solution, containing a little sodium thiosulphate. A small quantity of oil, not soluble in the carbon tetrachloride, was brought into solution by addition of some chloroform, and the solution was dried (Na_2SO_4) and evaporated to an oil (4·7 g.). This was dissolved in methanol (12 c.c.), and the solution was cooled to 0°, and kept thereat overnight. The solid (2·1 g.; m. p. 85—100°) was collected and recrystallised from methanol to give the first *dibromide* as hexagonal plates, m. p. 111—112°, $[\alpha]_D^{20}$ +43·8° (*c*, 1·1 in chloroform) (Found: C, 35·5; H, 4·3; Br, 33·1. $C_{14}H_{20}O_9Br_2$ requires C, 35·3; H, 4·2; Br, 33·6%).

The main methanolic filtrate was evaporated to a solid residue, which on recrystallisation twice from light petroleum (b. p. 60—80°) and four times from ethyl acetate–light petroleum (b. p. 60—80°) gave cubes of the isomeric *dibromide*, m. p. 76°, $[\alpha]_D^{20}$ +45·5° (*c*, 1·1 in chloroform) (Found: C, 35·3; H, 4·3; Br, 33·6%).

The first dibromide (1·3 g.; crude) was heated under reflux with a solution of potassium thiolacetate (0·9 g.) in ethanol (15 c.c.) for 8 hours. The bisthiolacetate was isolated in the usual way and formed a syrup (1·1 g.), $[\alpha]_D^{20}$ +25·4° (*c*, 2·6 in chloroform), which failed to crystallise. Light absorption: max. 2290 A., ε = 6500. The second dibromide (1·9 g.), similarly treated, also gave a syrup (1·6 g.), $[\alpha]_D^{20}$ +21·8° (*c*, 3·0 in chloroform); light absorption: max. 2290 A., ε = 7000.

Reaction of Tetra-acetyl 1 : 2-*Mannitoleen with Hypobromous Acid*.—The tetra-acetate (0·27 g.), *N*-bromosuccinimide (0·19 g.), water (7 c.c.), and ether (3 c.c.) were shaken together for 17 hours. The ethereal layer was removed, and the aqueous portion was extracted twice with ether. The combined extracts were dried (Na_2SO_4) and evaporated. The crude bromohydrin (0·35 g.) was heated with acetic acid (1 c.c.), acetic anhydride (1 c.c.), and fused sodium acetate (0·25 g.) for 24 hours on the steam-bath. The reaction mixture was cooled, shaken with water for some time, and extracted with chloroform. The extracts were washed ($NaHCO_3$ solution), dried (Na_2SO_4), and evaporated to a syrup, which partly crystallised. The solid was removed and washed with ethanol–light petroleum (b. p. 40—60°), to give hexa-acetyl sorbitol, (0·08 g.), m. p. and mixed m. p. 96—98°, $[\alpha]_D^{20}$ +9·0° (*c*, 1·0 in chloroform).

3 : 4-*Dimethanesulphonyl* 1 : 2-5 : 6-*Diisopropylidene Mannitol*.—To a solution of methansulphonyl chloride (7·15 g.) in dry pyridine (15 c.c.), cooled in ice, was added powdered 1 : 2-5 : 6-diisopropylidene mannitol (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338) (6·6 g.), during *ca.* 5 minutes. After being kept at 0° overnight, the mixture was diluted with water (200 c.c.). The precipitated solid was collected, washed with water, and recrystallised from methanol to give the *dimethanesulphonate* (9·0 g.), m. p. 143—144°, $[\alpha]_D^{20}$ −5·2 (*c*, 2·4 in chloroform) (Found: C, 39·7; H, 6·3. $C_{14}H_{26}O_{10}S_2$ requires C, 40·2; H, 6·3%).

Reactions of the 3 : 4-*Disulphonates with Sodium Iodide*.—(*a*) 3 : 4-Ditosyl 1 : 2-5 : 6-diisopropylidene mannitol (Brigl and Grüner, *Ber.*, 1934, **67**, 1969) (2·9 g.), sodium iodide (6·0 g.), and acetone (40 c.c.) were heated in a sealed tube for 2 hours at 80°; no reaction occurred. Heating was continued for 12 hours at 110°; iodine was then liberated, and from the cooled reaction product the theoretical amount of sodium toluene-*p*-sulphonate (1·9 g.) was removed by filtration. The filtrate was worked up as previously described, but gave only a trace of dark oil from the chloroform extracts.

(*b*) The corresponding 3 : 4-dimethanesulphonate (12·5 g.), sodium iodide (36 g.), and acetone (250 c.c.) were heated in a pressure bottle at 100° for 55 hours. The precipitated sodium methanesulphonate amounted to only 2·2 g. (23%); the dark filtrate, containing free iodine, was returned to the bottle and heated for 15 hours at 125—135°. The reaction had now gone to completion (total yield of sodium methanesulphonate, 9·5 g.), and the mixture was worked up as before. The only identifiable product from the chloroform extractions was mesityl oxide.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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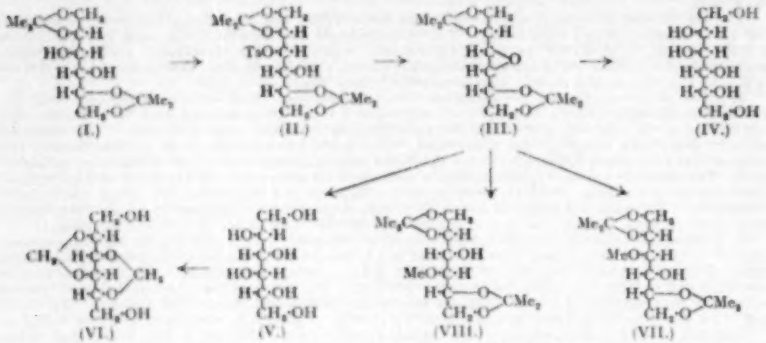
114. 1 : 2-5 : 6-*Diisopropylidene* 3 : 4-*Anhydro*-D-*talitol*.

By Peter Bladon and L. N. Owen.

The preparation of 1 : 2-5 : 6-*diisopropylidene* 3 : 4-*anhydro*-D-*talitol* from 3-*tosyl* 1 : 2-5 : 6-*diisopropylidene* **mannitol** is described. This anhydro-compound is the first non-terminal hexitol derivative of the ethylene oxide type to be obtained. Although the anhydro-ring is more stable than when it is attached to a terminal carbon atom, it is broken by acid hydrolysis, to give a mixture of D-mannitol and D-iditol, and also by treatment with alkoxides under vigorous conditions.

Derivatives of only three anhydro-hexitols of the ethylene oxide type have hitherto been described, *viz.*, 1-tosyl 2 : 4-benzylidene and 1 : 3-2 : 4-diethylidene 5 : 6-anhydrosorbitol (Vargha, *Ber.*, 1935, **68**, 1377; Vargha and Puskás, *Ber.*, 1943, **76**, 859; Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837; Wiggins, *J.*, 1946, 388); 1 : 2-3 : 4-di*iso*propylidene 5 : 6-anhydromannitol (Wiggins, *loc. cit.*); and 3 : 4-*iso*propylidene and 3 : 4-ethylidene 1 : 2-5 : 6-dianhydromannitol (Wiggins, *J.*, 1946, 384). In all these, the oxide rings engage terminal carbon atoms and are readily opened either by acid hydrolysis or by treatment with alkoxides or organic bases; the ring fission occurs usually between the oxygen atom and the terminal carbon atom, so that no change of configuration results. For example, 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol on acid hydrolysis gives only mannitol, and with sodium methoxide only 1 : 6-dimethyl 3 : 4-*iso*propylidene mannitol is obtained. The sole exception to this generalisation is provided by 1-tosyl 2 : 4-benzylidene 5 : 6-anhydrosorbitol, which on acid hydrolysis gives 1-tosyl 2 : 5-anhydro-L-iditol by Walden inversion at $C_{(5)}$ (Vargha and Puskás, *loc. cit.*).



In connection with the synthesis of polyhydroxy-dithiols, the 5 : 6-anhydro-derivatives of mannitol and of sorbitol have been used for the preparation of the 6-allyl ethers, by effecting ring fission with sodium allyl oxide in allyl alcohol (Bladon and Owen, Part VI, *J.*, 1950, 591). As part of a possible route for the synthesis of non-terminal allyl ethers of polyhydric alcohols, a non-terminal epoxide was required, and, since anhydro-compounds of the ethylene oxide type are most conveniently prepared from tosyl compounds (cf. Peat, " Advances in Carbohydrate Chemistry," **2**, 37), attempts were made to form the monotosyl derivative (II) of 1 : 2-5 : 6-di*iso*propylidene mannitol (I). When this compound was treated with 1 mole of toluene-*p*-sulphonyl chloride in pyridine, a syrup was obtained from which 3 : 4-ditosyl 1 : 2-5 : 6-diisopropylidene mannitol (Brigl and Grüner, *Ber.*, 1934, **67**, 1969) could be separated by crystallisation from methanol, and from which, on one occasion, crystalline 3-*tosyl* 1 : 2-5 : 6-*diisopropylidene mannitol* (II) was also obtained. Subsequent attempts to isolate this mono-derivative from the reaction mixture were unsuccessful, but such isolation proved to be unnecessary, since treatment of the crude reaction product, in chloroform, with cold methanolic sodium methoxide gave an oil, from which the ditosyl compound (unaffected by this treatment) was precipitated by light petroleum; distillation of the material soluble in this solvent then gave crystalline 1 : 2-5 : 6-*diisopropylidene* 3 : 4-*anhydro*-D-*talitol* (III).

The configuration allocated to this compound is in conformity with the knowledge that, in the formation of an epoxide from a tosyl compound, a Walden inversion occurs on the carbon

atom carrying the sulphonyloxy-group; it was also confirmed by the following observations. Acid hydrolysis of the epoxide resulted in fission of the ring and loss of the isopropylidene residues, and gave a mixture of hexitols from which mannitol (IV) was isolated by crystallisation. The material in the mother-liquors, on treatment with formaldehyde and concentrated hydrochloric acid, gave a dimethylene hexitol, the properties of which agreed with those given by Hann and Hudson (*J. Amer. Chem. Soc.*, 1945, **67**, 602) for 2 : 4-3 : 5-dimethylene L-iditol, except that the optical rotation was of opposite sign. Accordingly, the product is formulated as 2 : 4-3 : 5-*dimethylene* D-*iditol* (VI), formed from D-iditol (V) resulting from the hydrolysis of the anhydro-compound. Acetylation of (VI) gave 1 : 6-*diacetyl* 2 : 4-3 : 5-*dimethylene* D-*iditol* which likewise had properties, differing only in the sign of rotation, similar to those recorded by Hann and Hudson (*loc. cit.*) for the enantiomorph. The production of both D-mannitol and D-iditol from the anhydro-compound can be explained only by assigning to it the D-talitol configuration; ring-opening thus occurs in two directions, leading (with inversion on $C_{(3)}$) to the mannitol configuration and (with inversion on $C_{(4)}$) to the iditol configuration.

1 : 2-5 : 6-Di*iso*propylidene 3 : 4-anhydro-D-talitol, the first non-terminal epoxide in the hexitol series, was noticeably more resistant than terminal epoxides to attack by alkoxides, being recovered largely unchanged after being heated under reflux with 0·2N-methanolic sodium methoxide, conditions under which terminal epoxides are readily opened (Vargha and Puskás, *loc. cit.*). With 3·5N-methanolic sodium methoxide at 100°, however, it gave a mixture of 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol (VII) and (probably) 3(or 4)-methyl 1 : 2-5 : 6-di*iso*propylidene D-iditol (VIII), from which, by acid hydrolysis, 3-methyl mannitol was obtained, identical with the compound prepared by Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 70) by reduction of 3-methyl mannose. It was not possible to isolate the 3-methyl iditol which presumably was also present.

Similarly, on being heated with sodium allyl oxide in allyl alcohol at 100°, the epoxide gave a mixture of 3-allyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol and (probably) 3-allyl 1 : 2-5 : 6-di*iso*propylidene D-iditol. Acid hydrolysis then gave a mixture of allyl hexitols from which 3-allyl D-mannitol was isolated, identical with the material obtained by direct allylation of 1 : 2-5 : 6-di*iso*propylidene mannitol (Bladon and Owen, *loc. cit.*).

Experimental.

3-*Tosyl* 1 : 2-5 : 6-Di*iso*propylidene *Mannitol*.—A solution of 1 : 2-5 : 6-di*iso*propylidene mannitol (52·4 g., 0·2 mol.) (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338) in dry pyridine (200 c.c.) was stirred vigorously and cooled during the addition of a solution of toluene-*p*-sulphonyl chloride (40 g., 0·21 mol.) in dry pyridine (100 c.c.) during 2½ hours, the temperature being kept below 2°. After the mixture had remained for 20 hours at room temperature, the greater part of the pyridine was removed by distillation under reduced pressure. The syrupy residue was taken up in chloroform (250 c.c.) and treated with crushed ice (300 g.). The chloroform layer was separated and the aqueous solution was extracted twice more with chloroform. The extracts were washed with water, dilute sulphuric acid, and finally with sodium hydrogen carbonate solution, and then dried (Na_2SO_4). The solvent was removed by distillation, leaving a syrup (66·1 g.) which was, in general, used without further treatment for the next stage. In one experiment, however, a portion (4·5 g.) of this crude monotosyl derivative was crystallised from methanol; the first crop of solid consisted of 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol, m. p. and mixed m. p. 118—119°. Treatment of the methanolic mother-liquors with water gave a solid (2·6 g.), m. p. 75—90°; this was dissolved in ethyl acetate, and the solution was dried (Na_2SO_4), concentrated to small volume, and treated with light petroleum (b. p. 60—80°) to give a solid, m. p. 98—100°. Further recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave 3-*tosyl* 1 : 2-5 : 6-*diisopropylidene mannitol*, m. p. 100°, $[\alpha]_D^{20}$ −27° (*c*, 0·9 in chloroform) (Found : C, 54·6; H, 6·6. $C_{19}H_{28}O_8S$ requires C, 54·8; H, 6·8%). Attempts to isolate this compound on other occasions were unsuccessful; furthermore, the analytically pure material decomposed after a few weeks to a viscid mass, which was acidic and contained free acetone.

1 : 2-5 : 6-*Diisopropylidene* 3 : 4-*Anhydro*-D-*talitol*.—To a solution of the crude 3-tosyl di*iso*propylidene mannitol syrup (60 g.) in chloroform (240 c.c.), cooled in ice, was added a solution of sodium (3·5 g.) in dry methanol (150 c.c.), with shaking and cooling. The sodium toluene-*p*-sulphonate first separated as a gel, which later crystallised. The mixture was left overnight at 0° and was then treated with water (500 c.c.). The chloroform layer was separated, and the aqueous portion was extracted thrice with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to a syrup (37·6 g.), which was dissolved in boiling light petroleum (b. p. 60—80°; 100 c.c.); the solid which separated on cooling was collected and extracted twice more with light petroleum. The insoluble material (15 g.) was recrystallised from methanol (100 c.c.) and gave long needles of 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol (8·5 g.), m. p. 118°, $[\alpha]_D^{20}$ +7·8° (*c*, 2·5 in chloroform) (Found : C, 54·8; H, 5·9. Calc. for $C_{33}H_{44}O_{12}S_2$: C, 54·7; H, 6·0%). Brigl and Grüner (*Ber.*, 1934, **67**, 1969) give m. p. 120—121°, $[\alpha]_D$ +9·3° (in chloroform).

Evaporation of the petroleum solution under reduced pressure gave a crystalline residue (25 g.) which was distilled at 80—140° (air-bath)/0·0001 mm.; the distillate (20·7 g.) solidified in the form of large plates, m. p. 49—53°. Recrystallisation from aqueous methanol gave large granular crystals of

1 : 2-5 : 6-*diisopropylidene* 3 : 4-*anhydro*-D-*talitol*, m. p. 54—56°, $[\alpha]_D^{20}$ −16·2° (*c*, 1·5 in chloroform) (Found : C, 59·3; H, 8·1. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·3%). The overall yield of the anhydro-compound from diisopropylidene mannitol was 43%.

Acid Hydrolysis of 1 : 2-5 : 6-*Diisopropylidene* 3 : 4-*Anhydro*-D-*talitol*.—The compound (4·9 g.) was heated on the steam-bath with 0·9*N*-sulphuric acid (5 c.c.) for 2½ hours, the liberated acetone being allowed to escape. The cooled solution was then extracted once with ether, to remove a trace of oily impurity, and treated with a slight excess of barium hydroxide solution, the excess then being neutralised with carbon dioxide. The precipitate was removed on the centrifuge and washed twice with a little water. Evaporation of the aqueous solution under reduced pressure then gave a syrup, which was evaporated several times with ethanol and then dissolved in ethanol (45 c.c.) and water (4 c.c.). This solution was filtered and concentrated to small bulk; successive treatments with small quantities of ethyl acetate then gave three crops of mannitol, m. p. 163—166°, 160—161°, and 161—163°, respectively, undepressed on admixture with authentic mannitol of m. p. 166° (iditol has m. p. 73—74°). The total yield was 1·83 g. Evaporation of the mother-liquors gave a syrup (2·0 g.), which contained iditol (see below).

2 : 4-3 : 5-*Dimethylene* D-*Iditol*.—The syrup (2·0 g.) was heated on the steam-bath with 40% aqueous formaldehyde solution (5 c.c.) and concentrated hydrochloric acid (5 c.c.) for 6 hours, and then left overnight at room temperature. The solution was filtered and evaporated on the steam-bath to a syrup, which was dissolved in a little water and again evaporated to yield a solid residue. This was dissolved in boiling water (10 c.c.), and the solution was filtered; on cooling, a crystalline solid separated, m. p. 262—265° (0·52 g.), and on further recrystallisation from water and from aqueous methanol (with charcoal) small plates of 2 : 4-3 : 5-*dimethylene* D-*iditol* were obtained, having m. p. 262—265° (decomp.), $[\alpha]_D^{20}$ −38·5° (*c*, 0·3 in water) Found : C, 46·25; H, 6·6. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%). Hann and Hudson (*loc. cit.*), for the L-form, recorded m. p. 260—262° (decomp.), $[\alpha]_D^{20}$ +39·2° in water.

The mother-liquors from the above crystallisations were re-treated with formaldehyde and hydrochloric acid, and gave a further small quantity of dimethylene D-iditol.

1 : 6-*Diacetyl* 2 : 4-3 : 5-*Dimethylene* D-*Iditol*.—2 : 4-3 : 5-Dimethylene D-iditol (0·2 g.) was dissolved in a mixture of acetic acid (0·6 c.c.) and acetic anhydride (1·4 c.c.). Concentrated sulphuric acid (0·05 c.c.) was added, and after a few minutes the reaction mixture was poured into water. The precipitated solid was recrystallised first from ethanol and finally from water, and gave needles (0·1 g.) of the *diacetyl* derivative, m. p. 220—221°, $[\alpha]_D^{20}$ +4·8° (*c*, 0·9 in chloroform) (Found : C, 49·7; H, 6·1. $C_{12}H_{18}O_8$ requires C, 49·65; H, 6·25%). Hann and Hudson (*loc. cit.*), for the L-enantiomorph, give m. p. 219—220°, $[\alpha]_D^{20}$ −3·9° in chloroform.

Reaction of 1 : 2-5 : 6-*Diisopropylidene* 3 : 4-*Anhydro*-D-*talitol with Sodium Methoxide*.—Heating of the anhydro-compound with 0·2*N*-methanolic sodium methoxide under reflux for periods up to 15 hours resulted in no significant change in optical rotation, and the material was recovered almost quantitatively from the solution. With 2*N*-methanolic sodium methoxide in a sealed tube at 100°, a change in $[\alpha]_D$ from −23·2° (initial) to +5·1° (6 hours) was observed.

The anhydro-compound (5 g.) was therefore dissolved in 3·5*N*-methanolic sodium methoxide (35 c.c.; and the solution was heated in a small autoclave at 100—105° for 20 hours. The cooled product was diluted with water, neutralised with carbon dioxide, and concentrated under reduced pressure to remove most of the methanol. The aqueous solution was then extracted with ether (5 × 50 c.c.), the extracts were dried (Na_2SO_4), and the solvent was evaporated. Distillation of the residual syrup (5·0 g.) gave a colourless liquid, probably a mixture of 3-methyl 1 : 2-5 : 6-diisopropylidene D-mannitol and 3-methyl 1 : 2-5 : 6-diisopropylidene D-iditol, b. p. 96°/0·003 mm., n_D^{25} 1·4530, $[\alpha]_D^{25}$ +6·8° (*c*, 4 in chloroform) (Found : C, 56·5; H, 8·6. Calc. for $C_{13}H_{22}O_6$: C, 56·5; H, 8·8%). A diisopropylidene compound of uncertain structure from 3-methyl mannitol, prepared by Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 70), had m. p. 57—58°, $[\alpha]_D^{20}$ +9·0° (in alcohol).

3-*Methyl Mannitol*.—The above mixture was hydrolysed by being heated with 0·45*N*-sulphuric acid (10 c.c.) for 7 hours, the acetone being removed from the liquid by the passage of a slow stream of nitrogen. The solution was extracted once with ether, to remove oily impurities, and it was then heated to *ca.* 80° and treated with a slight excess of barium hydroxide solution, the excess then being removed with carbon dioxide. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to a syrup, which was dried by evaporation several times with ethanol. It was then dissolved in hot ethanol (20 c.c.) and filtered from a small amount of insoluble matter. Evaporation then gave a syrup (2·7 g.; calc. yield of methyl hexitol, 2·8 g.) which on treatment with ethanol–ethyl acetate gave a precipitate of 3-methyl mannitol monohydrate (1·25 g., 45%), m. p. 85—86°. Haskins, Hann, and Hudson (*loc. cit.*) give m. p. 86—87°. Crystallisation from dry ethanol gave the anhydrous 3-methyl mannitol, m. p. 132—133°, $[\alpha]_D^{20}$ +16·5° (*c*, 2 in water). Haskins *et al.* (*ibid.*) give m. p. 133—134°, $[\alpha]_D^{20}$ +16·7° (*c*, 2 in water).

Evaporation of the mother-liquors from the initial precipitation of 3-methyl mannitol gave a syrup (1·4 g.) which could not be induced to crystallise, and presumably contained 3-methyl iditol.

3-*Allyl* D-*Mannitol*.—When 3 : 4-anhydro-D-talitol was heated with 0·1*N*-sodium allyl oxide in allyl alcohol for 5½ hours under reflux, the greater part of the material was recovered unchanged. A solution of the anhydro-compound (6·1 g.) in dry allyl alcohol (50 c.c.) containing sodium (5 g.; *i.e.*, a 4*N*-solution) was heated under an air reflux condenser for 17 hours, during which time the solution became more concentrated owing to loss of solvent. The syrupy product was treated with water (100 c.c.) and steam-distilled to remove allyl alcohol. The alkali was neutralised with carbon dioxide, and the solution was extracted with ether (4 × 60 c.c.). The dried (Na_2SO_4) extracts were then evaporated and the residual oil was distilled to give a mixture (7·0 g., 94%) of 3-allyl 1 : 2-5 : 6-diisopropylidene D-mannitol and 3-allyl 1 : 2-5 : 6-diisopropylidene D-iditol, b. p. 94—97°/0·001 mm., n_D^{25} 1·4634, $[\alpha]_D^{25}$ +4·1° (*c*, 2 in chloroform) (Found : C, 59·85; H, 8·4. Calc. for $C_{12}H_{20}O_6$: C, 59·6; H, 8·7%). This mixture was hydrolysed in a similar way to that used for the corresponding methyl compounds and gave 3-allyl D-mannitol (1·6 g., 30%), m. p. and mixed m. p. 117—118°, $[\alpha]_D^{20}$ +17·7° (*c*, 1 in water) (cf. Bladon and

Owen, *J.*, 1950, 591). Evaporation of the mother-liquors gave a syrup (1·75 g.) from which no crystalline material could be obtained.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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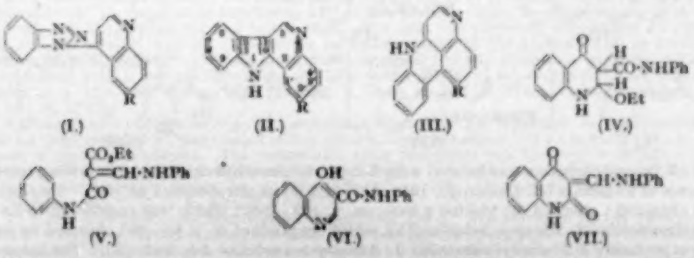
115. *Attempts to Find New Antimalarials. Part XXIX. The Synthesis of Various Derivatives of* 2 : 3-*Benz-γ-carboline.*

By WILLIAM O. KERMACK and (MRS.) NORA E. STOREY.

The Graebe–Ullmann method has been used to synthesise 2 : 3-benz-γ-carboline (II; R = H) and a number of its derivatives. Treatment of 2 : 3-benz-γ-carboline with 2-diethylaminoethyl chloride in nitrobenzene yields 4-2″-*diethylaminoethyl*-2 : 3-*benz-γ-isocarbeline* (X), whilst in toluene in presence of sodamide the product of the reaction is 1-2″-*diethylaminoethyl*-2 : 3-*benz-γ-carboline* (IX). The structure of (IX) has been confirmed by the synthesis of its dimethiodide (XII) from 4-*methyl*-2 : 3-*benz-γ-isocarboline* (XI) and 2-diethylaminoethyl chloride, followed by treatment of the resulting 4-methyl-1-2″-diethylaminoethyl-2 : 3-benz-γ-carbolinium chloride, first with potassium iodide and then with methyl iodide. Two by-products isolated by Schofield and Simpson in the preparation of ethyl 4-hydroxyquinoline-3-carboxylate from aniline and ethyl ethoxymethylenemalonate have been identified.

A NUMBER of derivatives of 2 : 3-benz-γ-carboline containing a methyl group in position 5 have been synthesized by Kermack and Smith (*J.*, 1930, 1999). Clemo and Perkin (*ibid.*, 1924, **125**, 1608) treated the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-4-quinolone with 20% sulphuric acid and instead of the expected 4 : 5-dihydro-2 : 3-benz-γ-carboline, $C_{18}H_{12}N_2$, isolated a compound, $C_{15}H_{10}N_2$, m.p. >320°, which they assumed to be 2 : 3-benz-γ-carboline (indolo-3′ : 2′-3 : 4-quinoline) itself. During investigations on the constitution of indigo-yellow, de Diesbach, de Bie, and Rubli (*Helv. Chim. Acta*, 1934, **17**, 113) isolated a degradation product, m. p. 332°, which they considered on the basis of oxidation experiments to be 2 : 3-benz-γ-carboline. It seemed desirable to synthesise this base by an unambiguous method and at the same time to prepare a number of derivatives carrying basic side chains in order that they might be subjected to biological tests.

The method employed was a modification of the Graebe–Ullmann carbazole synthesis used by Kermack and Smith in their synthesis of the 5-methyl derivatives of 2 : 3-benz-γ-carboline (*loc. cit.*). Thus 4-chloroquinoline was condensed with *o*-phenylenediamine, and the resulting 4-*o-aminoanilinoquinoline* treated with nitrous acid to yield the *benztriazole* derivative (I; R = H). When heated in syrupy phosphoric acid this compound lost nitrogen and underwent the Graebe–Ullmann reaction to yield 2 : 3-benz-γ-carboline (II; R = H). Here it is assumed that cyclization occurs so as to involve position 3 of the quinoline nucleus, although it might occur at position 5 to yield the isomeric compound (III). The latter course is excluded not only by the properties of the product, but also by the experiments in the 5-methyl series (Kermack and Smith, *loc. cit.*).



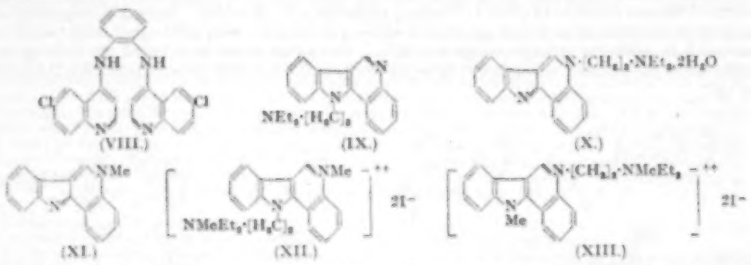
4-Chloroquinoline was prepared from aniline and ethyl ethoxymethylenemalonate (cf. Schofield and Simpson, *J.*, 1946, 1033, and Price and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1204). When somewhat impure ethyl ethoxymethylenemalonate was employed cyclization of

the crude intermediate ethyl anilinomethylenemalonate in liquid paraffin at 250° yielded three crystalline products. One of these was ethyl 4-hydroxyquinoline-3-carboxylate; the other two melted at 118° and 318° respectively and were evidently identical with Schofield and Simpson's by-products, $C_{18}H_{14}O_3N_2$ and $C_{18}H_{12}O_2N_2$ respectively (*loc. cit.*). Schofield and Simpson suggested for the lower-melting compound formula (IV) or (V) and for the higher-melting compound the formula (VI) or (VII), the last compound being formed from (V) by the loss of a molecule of ethanol. The following observations decide the constitution of these two products.

The compound, m. p. 118°, when heated in diphenyl was converted into the compound, m. p. 318°, with loss of ethanol. The compound, m. p. 318°, when boiled with acid yielded 4-hydroxyquinoline-3-carboxylic acid and also a diazotisable amine, presumably aniline. This strongly suggests that the compound is *4-hydroxyquinoline-3-carboxyanilide* (VI), which is confirmed by its synthesis from equimolecular amounts of ethyl 4-hydroxyquinoline-3-carboxylate and aniline. As (VI) is formed from the lower-melting compound with the loss of a molecule of alcohol, it appears very probable that the latter has the formula (V) and not (IV), which is confirmed by its synthesis from equimolecular amounts of ethyl anilinomethylenemalonate and aniline.

In contrast to Schofield and Simpson (whose product did not crystallise) and Price and Roberts (who obtained a product which set to a crystalline mass between −12° and −15°) we found that *p*-anisidine and ethyl ethoxymethylenemalonate, when heated on a steam-bath, yielded a crystalline compound, m. p. 38—40°; its analyses were in accord with its formulation as *ethyl* p-*anisidinomethylenemalonate* and it was converted into 4-chloro-6-methoxyquinoline by the series of reactions described by Price and Roberts.

From 4-chloro-6-methoxyquinoline and *o*-phenylenediamine, *4-o-aminoanilino-6-methoxyquinoline* was obtained, which with nitrous acid yielded the *benztriazole* derivative (I; R = OMe). This, when heated in syrupy phosphoric acid, afforded *2′-methoxy-2 : 3-benz-γ-carboline* (II; R = OMe). From 4 : 6-dichloroquinoline by an analogous series of reactions, there was obtained *2′-chloro-2 : 3-benz-γ-carboline* (II; R = Cl). On one occasion in the preparation of 2′-methoxy-2 : 3-benz-γ-carboline, *6-methoxy-4-(benztriazol-1-yl)quinoline*, when heated in syrupy phosphoric acid, yielded *4-anilino-6-methoxyquinoline*, the identity of which was confirmed by its synthesis from 4-chloro-6-methoxyquinoline and aniline. The special conditions responsible for the reaction taking this abnormal course were not ascertained; it would seem that some reducing agent must inadvertently have been present. A by-product isolated on one occasion from the reaction between 4 : 6-dichloroquinoline and *o*-phenylenediamine proved to be *NN′-di-(6-chloro-4-quinolyl)-o-phenylenediamine* (VIII), the structure of which was confirmed by its synthesis from *6-chloro-4-o-aminoanilinoquinoline* and 4 : 6-dichloroquinoline. (VIII) yielded a *dimethiodide* when boiled in nitrobenzene with excess of methyl sulphate and then treated with potassium iodide.



2 : 3-Benz-γ-carboline was treated with 2-diethylaminoethyl chloride (*a*) in boiling toluene in presence of sodamide (cf. Dewar, *J.*, 1944, 619) and (*b*) in nitrobenzene at 100°. Two products were obtained: method (*a*) yielded a base, m. p. 103—104°, which was considered to be *1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline* (IX), whilst the product, m. p. 84—86°, obtained by method (*b*) was probably *4-2″-diethylaminoethyl-2 : 3-benz-γ-isocarboline dihydrate* (X). The latter compound, even after prolonged drying, contained a molecule of water, so that it may clearly be either the carbolinium hydroxide (in its ionic form or as the pseudo-base), or the monohydrate of the anhydronium base; it is relatively soluble in both benzene and light petroleum, and readily

forms a dimethiodide, one of the methyl groups of which is undoubtedly attached at $N_{(1)}$ (see below); it thus behaves as the anhydronium base rather than as the quaternary hydroxide, and this conclusion is confirmed by the fact that the analogous compound derived from 2′-chloro-2 : 3-benz-γ-carboline, when dried, forms first a compound of similar composition to that above, and then yields the anhydrous anhydronium base. However, the distinction between a hydrated anhydronium base and a quaternary hydroxide is not sharp, as the hydrated anhydronium base with a hydrogen atom co-ordinated at $N_{(1)}$ is scarcely distinguishable from the quaternary hydroxide.

When treated with excess of methyl iodide and nitrobenzene the bases (IX) and (X) yielded dimethiodides, m.p. 276—278° and 263—264° respectively. The dimethiodide, m. p. 276—278°, was also prepared as follows: from the *methiodide* of 2 : 3-benz-γ-carboline, the anhydronium base, *4-methyl-2 : 3-benz-γ-isocarboline* (XI), was obtained by treatment with alkali; when this compound was warmed in nitrobenzene with 2-diethylaminoethyl chloride and the product treated with potassium iodide, a compound, m. p. 225°, was isolated which, on treatment with methyl iodide, yielded a compound, m. p. 276—278°, identical with the dimethiodide in question. In this second method of synthesis one methyl group is certainly located at $N_{(9)}$: it has been amply proved that, when alkylisocarbolines are treated with alkyl halides, the second alkyl group becomes attached to $N_{(1)}$. It follows that the diethylaminoethyl group is here attached to $N_{(1)}$, so that the dimethiodide in question must have the structure (XII). This in turn proves that the product obtained by method (*a*) must have the constitution (IX), and the structure (X) of the product obtained by method (*b*) necessarily follows; the dimethiodide of (X) has presumably the structure (XIII).

Similarly, from 2′-chloro-2 : 3-benz-γ-carboline and 2-diethylaminoethyl chloride two compounds were obtained: under conditions (*a*) *2′-chloro-1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline*, and under conditions (*b*) *2′-chloro-4-2″-diethylaminoethyl-2 : 3-benz-γ-isocarboline*. From *2′-methoxy-2 : 3-benz-γ-carboline* conditions (*b*) afforded 2′-methoxy-4-2″-diethylaminoethyl-2 : 3-benz-γ-isocarboline, isolated as the *dinitrobenzoate*, but it was not possible to isolate a crystalline compound from the products obtained under conditions (*a*). A by-product encountered in the experiments carried out under conditions (*b*) was 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride, formed by the interaction of two molecules of 2-diethylaminoethyl chloride. It was identified as its di-iodide, previously prepared by Gough and King (*J.*, 1928, 2436).

Experimental.

4-Hydroxyquinoline-3-carboxyanilide.—Ethyl 4-hydroxyquinoline-3-carboxylate (1 g.) was refluxed with aniline (1 g.) for 5 hours. On cooling the solution deposited shining white plates of the *anilide*, m. p. 316—318° (from acetic acid) (Found: C, 72·3; H, 4·6; N, 10·85. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·7; N, 10·6%).

Ethyl β-Anilino-α-phenylcarbamylacrylate.—Equimolecular amounts of ethyl anilinomethylenemalonate and aniline were heated together at 100° for 1 hour; the *product*, recrystallised from light petroleum, had m. p. 118° (Found: C, 69·4; H, 5·9; N, 9·3. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%).

Conversion of Ethyl β-Anilino-α-phenylcarbamylacrylate into 4-Hydroxyquinoline-3-carboxyanilide.—Ethyl β-anilino-α-phenylcarbamylacrylate (0·5 g.) was heated in boiling diphenyl under reflux for 30 minutes. The diphenyl was extracted with ether to leave a solid residue, m. p. 315°. After crystallisation from glacial acetic acid, this product showed no depression in m. p. when mixed with a sample of 4-hydroxyquinoline-3-carboxyanilide.

4-o-Aminoanilinoquinoline.—4-Chloroquinoline (3·2 g.) (cf. Price and Roberts, *loc. cit.*) and *o*-phenylenediamine (2·1 g.) were heated together at 140° at 20—30 mm. After 10—20 minutes a brisk reaction occurred, and the solution set to a brittle resin. The solid was extracted with boiling N-hydrochloric acid and the solution filtered. The filtrate on cooling deposited the hydrochloride as greyish-white crystals, m. p. 285—290°. The *base* precipitated by alkali from an aqueous solution of this salt was recrystallised from a mixture of benzene and light petroleum (b. p. 40—60°) and formed buff-coloured prisms, m. p. 165—166° (3·5 g., 76%) (Found: C, 76·4; H, 5·4; N, 17·4. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·8%).

4-(Benztriazol-1-yl)quinoline.—4-*o*-Aminoanilinoquinoline (3 g.), dissolved in N-hydrochloric acid (500 c.c.) and cooled to 5°, was treated with a solution of sodium nitrite (0·8 g.) in water (10 c.c.) until an excess of nitrite was present. The voluminous white precipitate was dissolved in boiling water, and *4-(benztriazol-1-yl)quinoline*, precipitated by the addition of alkali, was recrystallised from ethanol; it formed slender white prisms, m. p. 132—133° (2·2 g., 70%) (Found: C, 73·0; H, 4·2; N, 23·0. $C_{15}H_{10}N_4$ requires C, 73·2; H, 4·1; N, 22·8%).

2 : 3-Benz-γ-carboline.—4-(Benztriazol-1-yl)quinoline (10 g.) was heated in syrupy phosphoric acid (15 c.c.) until the evolution of nitrogen ceased. The greyish-white precipitate which separated from the cool solution on dilution and basification was filtered off, washed, and recrystallised from aqueous methanol; it formed irregular colourless prisms, m. p. 342° with sublimation (7 g., 77%) (Found: C, 82·3; H, 4·9; N, 12·55. Calc. for $C_{15}H_{10}N_2$: C, 82·55; H, 4·6; N, 12·8%). This compound is insoluble in benzene or ether, sparingly soluble in ethanol, and more soluble in methanol or pyridine. It dissolves readily in hot dilute hydrochloric acid to give a clear solution which on cooling deposits white

crystals of the hydrochloride, and in hot concentrated nitric acid to yield a yellow nitrate (cf. Clemo and Perkin, and de Diesbach, de Bie, and Rubli, *loc. cit.*). The base exhibits a violet fluorescence under the arc light in most solvents, but not in concentrated sulphuric acid, though the crude product showed a marked fluorescence in the cold (cf. Clemo and Perkin, *loc. cit.*).

From 2 : 3-benz-γ-carboline and excess of methyl iodide in nitrobenzene, after 2 hours on the steam-bath, needle-shaped crystals of the *methiodide* separated. The product, recrystallised from methanol containing a trace of sodium thiosulphate, had m. p. 297° (0·2 g., 72%) (Found: C, 53·4; H, 3·4; N, 7·5. $C_{16}H_{15}N_2I$ requires C, 53·3; H, 3·6; N, 7·8%).

When a trace of iodine dissolved in ethanol is added to the alcoholic solution of this methiodide, a dark red colour immediately develops. The crystals of the methiodide prepared in the absence of thiosulphate also tend to develop a reddish colour which deepens to black on storage. This colour which may be discharged by sodium thiosulphate is apparently due to the action of traces of iodine in the salt or in the crystals (cf. Kermack, Smith, and Spragg, *Proc. Roy. Soc.* (*Edin.*), 1929—1930, **50**, 243).

4-Methyl-2 : 3-benz-γ-isocarboline.—An aqueous solution of the above methiodide was rendered alkaline with aqueous ammonia, and the yellow solid which separated was recrystallised from dry benzene, giving yellow prisms of the *monohydrate*, m. p. 195° (Found: C, 76·75; H, 5·6. $C_{16}H_{12}N_2.H_2O$ requires C, 76·8; H, 5·6%). The anhydrous *base*, obtained by drying the monohydrate *in vacuo* at 80° over phosphoric oxide for 4 hours, had m. p. 195° (Found: C, 82·9; H, 5·0; N, 11·7. $C_{16}H_{12}N_2$ requires C, 82·75; H, 5·2; N, 12·1%).

4-2″-Diethylaminoethyl-2 : 3-benz-γ-isocarboline.—2 : 3-Benz-γ-carboline (0·54 g.) and 2-diethylaminoethyl chloride (0·5 g.) in nitrobenzene (100 c.c.) were heated at 100° under reflux for 9 hours and set aside at room temperature overnight. The solution was filtered from some 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride and diluted with light petroleum (b. p. 100—120°) to yield a brown precipitate which was filtered off. The aqueous solution of the product was basified with aqueous ammonia to give a yellow precipitate which, recrystallised from aqueous ethanol, had m. p. 84—86°. When dried in a vacuum over calcium chloride, the yellow needles changed to a highly viscous liquid. When an analytical specimen of the crystals was dried over phosphoric oxide at 80° in a vacuum, the loss of weight was 5·07%. The resulting viscous liquid gave the following analytical values: Found: C, 74·3; H, 7·35; N, 12·2%. $(C_{21}H_{23}N_3.1\frac{1}{2}H_2O$ requires C, 74·2; H, 7·5; N, 12·4%). It thus appears that the liquid is the monohydrate of the expected base and that the crystals, m. p. 84—86°, are a *dihydrate* (Required: $C_{21}H_{23}N_3.2H_2O \longrightarrow C_{21}H_{23}N_3.H_2O$, loss 5·09%).

Dimethiodide of 4-2″-Diethylaminoethyl-2 : 3-benz-γ-isocarboline.—From 4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline dihydrate (0·53 g.) and methyl iodide (0·24 g.) in nitrobenzene (10 c.c.), heated under reflux at 60° (for 30 minutes), needle-shaped crystals of a *dimethiodide* separated almost immediately. These were filtered off, washed with ether, and crystallised from boiling water, forming white feathery needles, m. p. 263—264° (Found: C, 45·75; H, 4·65; N, 6·6. $C_{21}H_{23}N_3.2CH_3I$ requires C, 45·9; H, 4·8; N, 6·9%). An aqueous solution of the salt gives no precipitate with aqueous ammonia or sodium hydroxide, indicating that an anhydronium base is not formed.

1-2″-Diethylaminoethyl-2 : 3-benz-γ-carboline.—2 : 3-Benz-γ-carboline (1·09 g.), 2-diethylaminoethyl chloride (1·01 g.), finely powdered sodamide (1·95 g.), and toluene (10 c.c.) were heated on an oil-bath at 70° for 30 minutes and then at 115° for 30 minutes, and finally refluxed at 110° for 4 hours. To the cold mixture, water was added and a small amount of insoluble 2 : 3-benz-γ-carboline removed by filtration. The toluene layer was separated and extracted with dilute acetic acid (5%). The acid extracts were basified with aqueous ammonia, and the resulting oily precipitate extracted with ether. After drying (K_2CO_3) and reduction of volume, fine crystals of the *1-2″-diethylaminoethyl* derivative separated; recrystallised from aqueous ethanol, this had m. p. 103—104° (0·96 g., 60%) (Found: C, 79·6; H, 7·1; N, 13·2. $C_{21}H_{23}N_3$ requires C, 79·5; H, 7·25; N, 13·25%).

Dimethiodide of 1-2″-Diethylaminoethyl-2 : 3-benz-γ-carboline.—The preceding base (0·5 g.), methyl iodide (0·3 g.), and nitrobenzene (10 c.c.) were heated together at 60° for 30 minutes; the white solid was washed with ether and recrystallised from methanol; this *dimethiodide* formed prisms, m. p. 276—278° (Found: C, 45·6; H, 5·1; N, 6·4. $C_{21}H_{23}N_3.2CH_3I$ requires C, 45·9; H, 4·8; N, 6·9%). Addition of aqueous ammonia or sodium hydroxide to its aqueous solution gave no precipitate.

Dimethiodide of 1-2″-Diethylaminoethyl-2 : 3-benz-γ-carboline from 4-Methyl-2 : 3-benz-γ-isocarboline.—4-Methyl-2 : 3-benz-γ-*iso*carboline (0·5 g.) and excess of 2-diethylaminoethyl chloride were heated in nitrobenzene (20 c.c.) for 6 hours under reflux and set aside at room temperature overnight. The cooled solution was filtered to remove some 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride and then diluted with light petroleum (b. p. 80—100°). The crystalline material which separated was washed with ether and dissolved in the minimum amount of water. This aqueous solution, treated with a saturated solution of potassium iodide, yielded a white precipitate which, recrystallised from ethanol, had m. p. 225°. This compound 4-methyl-1-2″-diethylaminoethyl-2 : 3-benz-γ-carbolinium iodide was treated with methyl iodide in nitrobenzene at 100°, and yielded 1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline dimethiodide (m. p. 276—278°), identical (mixed m. p.) with the compound prepared by the previous method.

Ethyl p-Anisidinomethylenemalonate.—The oil obtained by heating *p*-anisidine (31 g.) and ethyl ethoxymethylenemalonate (54 g.) for 45 minutes on the steam-bath was freed from alcohol and triturated with light petroleum. On long storage the oil solidified and, although difficult to purify, eventually recrystallised from light petroleum (b. p. 80—100°) in large irregular prisms, m. p. 39—40° (Found: C, 61·1; H, 6·2; N, 4·9. $C_{14}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·8%).

4-o-Aminoanilino-6-methoxyquinoline.—When 4-chloro-6-methoxyquinoline (cf. Price and Roberts, *loc. cit.*) (3·9 g.) and *o*-phenylenediamine (2·16 g.) were heated together at 140° under reduced pressure a brisk reaction took place and the mixture solidified. The solid was extracted with boiling water; the hot solution was filtered and basified with aqueous ammonia; recrystallised from benzene, the *compound* formed colourless rectangular plates, m. p. 192° (Found: C, 72·3; H, 5·5; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·85%).

6-Methoxy-4-(benztriazol-1-yl)quinoline.—To a solution of the preceding base (3·5 g.) in *N*-hydrochloric acid (100 c.c.), a solution of sodium nitrite (1·15 g. in 5 c.c. of water) was added until a slight excess

was present. The solution was set aside for 2 hours at room temperature, after which the precipitate of hydrochloride was filtered off. The *base* was precipitated from the hot aqueous solution of the hydrochloride by aqueous ammonia and, recrystallised from light petroleum (b. p. 80—100°), had m. p. 129—130° (Found: C, 70·2; H, 4·2; N, 20·5. $C_{16}H_{12}ON_4$ requires C, 69·6; H, 4·3; N, 20·3%).

2'-Methoxy-2 : 3-benz-γ-carboline.—6-Methoxy-4-(benztriazol-1-yl)quinoline (5 g.) was heated in syrupy phosphoric acid until the evolution of nitrogen ceased. The resulting reddish-brown solution was poured into a large volume of water, and aqueous ammonia added to precipitate a yellow gelatinous solid which was dried and purified through its *dihydrochloride*, m. p. 310° (Found: C, 57·5; H, 4·8; $C_{16}H_{12}ON_2,2HCl,0{\cdot}75H_2O$ requires C, 57·4; H, 4·65%). The *base*, regenerated from its hydrochloride and recrystallised from pyridine, had m. p. 315° (Found: C, 77·0; H, 4·8; N, 11·1. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

In one experiment the product of this reaction proved to be *4-anilino-6-methoxyquinoline* (Found: C, 76·4; H, 5·8. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%), which did not depress the m. p. of a specimen prepared as described below.

4-Anilino-6-methoxyquinoline.—Aniline (0·5 g.) and 4-chloro-6-methoxyquinoline (1 g.) were heated together at 100° in the presence of a trace of copper bronze for 3 hours. After cooling, the melt was dissolved in dilute hydrochloric acid from which 4-anilino-6-methoxyquinoline was precipitated by aqueous ammonia. Recrystallised from ethanol, it formed pale yellow prisms, m. p. 220° (Found: C, 76·5; H, 5·4; N, 10·9. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

2'-Methoxy-4-2''-diethylaminoethyl-2 : 3-benz-γ-isocarboline.—2'-Methoxy-2 : 3-benz-γ-carboline (0·5 g.) and 2-diethylaminoethyl chloride in nitrobenzene were heated at 100° for 6 hours. The precipitate obtained on dilution of the cold solution with light petroleum was dissolved in water and basified with aqueous sodium hydroxide, and the resulting yellow oil extracted with ether. The ethereal extract was dried (Na_2SO_4), and the solvent removed, leaving a yellow oil which did not crystallise. The *bis-3 : 5-dinitrobenzoate* of the compound, recrystallised from ethanol, formed white prisms, m. p. 265° (Found: C, 55·7; H, 4·0; N, 12·3. $C_{28}H_{23}ON_5,2C_7H_3O_6N_2$ requires C, 56·0; H, 4·3; N, 12·7%).

6-Chloro-4-o-aminoanilinoquinoline.—4 : 6-Dichloroquinoline (9·9 g.) and *o*-phenylenediamine (5·4 g.) were heated under the conditions used for the methoxy-derivative. No reaction took place, but in the presence of a trace of copper bronze reaction occurred. The product was worked up as described for the 6-methoxy-compound; the *base*, recrystallised from light petroleum, formed irregular plates, m. p. 186—187° (Found: C, 66·8; H, 4·35; N, 15·3. $C_{15}H_{12}N_4Cl$ requires C, 66·8; H, 4·45; N, 15·6%).

NN'-Di-(6-chloro-4-quinolyl)-o-phenylenediamine.—6-Chloro-4-*o*-aminophenylaminoquinoline (0·54 g.) and 4 : 6-dichloroquinoline (0·4 g.) were heated together under reduced pressure at 140° for 30 minutes in the presence of copper. The product was extracted with dilute hydrochloric acid (5%), and the solution basified, to yield a white precipitate of *NN'-di-(6-chloro-4-quinolyl)-o-phenylenediamine*; recrystallised from nitrobenzene, this formed white needles, m. p. 342—344° (Found: C, 67·2; H, 3·5; N, 12·75. $C_{24}H_{14}N_4Cl_2$ requires C, 66·8; H, 3·7; N, 13·0%). The compound was also occasionally obtained as a by-product (highly insoluble in ethanol) in the preparation of 6-chloro-4-*o*-aminoanilinoquinoline.

A solution of this pentacyclic compound (0·55 g.) in nitrobenzene was treated with methyl sulphate (1 g.) at 130° for 2 hours under reflux. When the product was set aside at room temperature a dark red oil separated which was extracted several times with water; the combined aqueous extracts were concentrated to small volume. Addition of a saturated solution of potassium iodide yielded a yellow precipitate of the *dimethiodide*, m. p. 330—332° (from water) (Found: C, 41·4; H, 3·2. $C_{24}H_{14}N_4Cl_2,2CH_3I,2H_2O$ requires C, 41·6; H, 3·5%). The aqueous solution, basified with concentrated sodium hydroxide solution, gave an orange precipitate.

6-Chloro-4-(benztriazol-1-yl)quinoline.—A solution of 6-chloro-4-*o*-aminoanilinoquinoline (6·7 g.) in 8-hydrochloric acid at 100° was treated with sodium nitrite as for the methoxy-analogue. After 2 hours' storage at room temperature, the white gelatinous precipitate of the hydrochloride was filtered off, and the *base* regenerated and recrystallised from ethanol; it yielded long white needles, m. p. 185—186° (Found: C, 64·1; H, 2·9; N, 19·7. $C_{15}H_9N_4Cl$ requires C, 64·2; H, 3·2; N, 19·9%).

2'-Chloro-2 : 3-benz-γ-carboline.—6-Chloro-4-(benztriazol-1-yl)quinoline (2 g.) was heated in boiling syrupy phosphoric acid (10 c.c.) until evolution of nitrogen ceased. *2'-Chloro-2 : 3-benz-γ-carboline*, obtained by basification of the diluted solution with aqueous ammonia, crystallised from pyridine in small white needles, subliming, without melting, at >360° (Found: C, 71·4; H, 3·4; N, 10·9. $C_{15}H_9N_2Cl$ requires C, 71·3; H, 3·6; N, 11·1%).

2'-Chloro-4-methyl-2 : 3-benz-γ-isocarboline.—From 2'-chloro-2 : 3-benz-γ-carboline (0·5 g.) and an excess of methyl iodide in nitrobenzene at 100°, a crystalline methiodide separated which, recrystallised from water, melted at 225°. An aqueous solution of this methiodide was basified with sodium hydroxide, to yield a yellow base which after being washed and dried was recrystallised from benzene. Dried in a vacuum at 80° for 4 hours over P_2O_5, *2'-chloro-4-methyl-2 : 3-benz-γ-isocarboline* melted at 245° (Found: C, 67·3; H, 4·3. $C_{16}H_{11}N_2Cl,H_2O$ requires C, 67·5; H, 4·55%).

2'-Chloro-4-2''-diethylaminoethyl-2 : 3-benz-γ-isocarboline.—A solution of 2'-chloro-2 : 3-benz-γ-carboline (0·25 g.) in nitrobenzene (50 c.c.) was heated with 2-diethylaminoethyl chloride (0·2 g.) for 9 hours. The precipitate which formed on cooling and storage overnight at room temperature was separated, dissolved in water, and treated with aqueous ammonia hydroxide. The *base*, thus formed, was a yellow solid, which, when recrystallised from ethanol, softened at 40° and melted at 69—71°. After drying in a vacuum over potassium hydroxide and recrystallisation from dry light petroleum (b. p. 60—80°) the product melted at 125—126° (Found: C, 71·4; H, 5·9; N, 11·8. $C_{21}H_{22}N_3Cl$ requires C, 71·7; H, 6·3; N, 11·95%).

2'-Chloro-1-2''-diethylaminoethyl-2 : 3-benz-γ-carboline.—2-Diethylaminoethyl chloride (0·14 g.), 2'-chloro-2 : 3-benz-γ-carboline (0·25 g.), and finely ground sodamide (0·03 g.) in toluene (10 c.c.) were heated at 70° for 30 minutes and then at 115° for a further 30 minutes, and refluxed at 110° for 4 hours. After the mixture had been cooled water was added, the insoluble material removed by filtration, and the toluene layer separated and extracted with 5% acetic acid, from which the base was precipitated by aqueous ammonia. The ethereal solution of the *base* was dried (K_2CO_3) and the solvent removed; the

residue, recrystallised from aqueous ethanol, had m. p. 114—115° (Found: C, 71·3; H, 5·95; N, 11·6. $C_{21}H_{29}N_4Cl$ requires C, 71·7; H, 6·3; N, 11·95%). This base is a white crystalline solid and depresses the m. p. of 2'-chloro-4-3''-diethylaminoethyl-2 : 3-benz-γ-isocarboline (m. p. 125—126°) described above.

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RESEARCH LABORATORY,
ROYAL COLLEGE OF PHYSICIANS, EDINBURGH. [*Received, October 31st,* 1949.]

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116. *Compounds related to Thiosemicarbazide. Part IV. 5-Amino-3-phenyl-1 : 2 : 4-triazoles.*

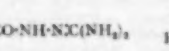
By ERIC HOGGARTH.

1-Benzoyl-*S*-methylisothiosemicarbazides (Part III) are cyclised by boiling with alcoholic solutions of organic bases to give a mixture of the 2-amino-5-phenyl-1 : 3 : 4-oxadiazole and 5-methylthio-3-phenyl-1 : 2 : 4-triazole. Piperidine differs from the other amines examined in giving also some of the 5-amino-3-phenyl-1 : 2 : 4-triazole. A new route to the amino-triazoles has been found in the reaction of *S*-methylisothiourea with benzhydrazides, followed by cyclisation of the resultant benzamidoguanidines.

ACCORDING to Benack (Dissert., Munich, 1896, quoted in "Beilstein," First Suppl. Vol., **26**, 45) 5-amino-3-phenyl-1 : 2 : 4-triazole (I; R = Ph) is formed by heating aminoguanidine carbonate with benzoyl chloride. This method was found unsatisfactory and it seemed possible that 1-benzoyl-*S*-methylisothiosemicarbazide (II; R = Ph) (Part III, *J.*, 1949, 1918) might react with ammonia or primary or secondary amines to give the benzamidoguanidine (III) or the corresponding alkyl derivatives of (III), which, it was expected, would be readily cyclised to 5-amino-3-phenyl-1 : 2 : 4-triazoles.

(I.)

(II.)


(III.)

(IV.)

(V.)

When (II; R = Ph) was heated with alcoholic ammonia, *iso*propylamine, or diethylamine, 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (IV; R = Ph) and 5-methylthio-3-phenyl-1 : 2 : 4-triazole (V; R = Ph) were formed in each case. The same reaction was observed when the tertiary bases, pyridine or triethylamine, were used. The *p*-anisoyl compound (II; R = *p*-MeO·C_6H_4) with ammonia or triethylamine gave the corresponding oxadiazole and triazole, but the amount of the latter product was small. *5-Methylthio-3-p-chlorophenyl-1 : 2 : 4-triazole* was obtained by the action of triethylamine on 1-*p*-chlorobenzoyl-*S*-methylisothiosemicarbazide and also by methylation of the corresponding thiol. These results are in contrast to the behaviour of 1-benzoyl-*S*-methylisothiosemicarbazides with alcoholic solutions of sodium alkoxides (Part III) which under similar conditions give 5-alkoxy-3-phenyl-1 : 2 : 4-triazoles. However, the crude alkoxy-triazoles, prepared in this way, were found to contain a small amount of sulphur which was difficult to remove by crystallisation and necessitated a method of purification involving dissolution in acids and alkalis. It is probable that small amounts of the methylthio-triazoles were formed in this reaction. Since the parent 1-benzoylthiosemicarbazides give the same product (*i.e.*, 3-phenyl-1 : 2 : 4-triazole-5-thiols) with alcoholic solutions of organic bases or sodium alkoxides (Part II, *J.*, 1949, 1163) it might be supposed that the 5-alkoxytriazoles were formed by the action of sodium alkoxides on 5-methylthio-triazoles. This was disproved by showing that 5-methylthio-3-phenyl-1 : 2 : 4-triazole was recovered unchanged after long refluxing with sodium ethoxide solution. The same methylthio-group has been shown (Part I, *J.*, 1949, 1160) not to be replaced on heating the substance with amines and it has now been observed that 5-methoxy-3-*p*-methoxyphenyl-1 : 2 : 4-triazole is not attacked by hot ammonia.

In the above reactions of 1-benzoyl-*S*-methylisothiosemicarbazides with amines, separation of the products was readily effected by dissolution of the triazole in sodium hydroxide solution. In each case, the crude triazole when precipitated from the clarified alkaline solution, had approximately the expected sulphur content. However, when piperidine was used as the amine, the triazole fraction had much less than half of the expected amount of sulphur and was eventually

separated into 5-methylthio-3-phenyl-1 : 2 : 4-triazole (V; R = Ph) and *5-piperidino-3-phenyl-1 : 2 : 4-triazole*, which have very similar solubilities.

Benzamidoguanidines (III; R = Ph, *p*-MeO·C$_6$H$_4$, or *p*-C$_6$H$_4$Cl) were obtained by warming the corresponding benzhydrazides with *S*-methylisothiourea sulphate and alkali, and the compound (III; R = Ph) was also obtained by treatment of aminoguanidine with benzoyl chloride in cold pyridine. These compounds are readily cyclised with loss of water on being heated just below their melting points and in this manner very satisfactory yields of *5-amino-3-phenyl-*, *5-amino-3-p-methoxyphenyl-*, and *5-amino-3-p-chlorophenyl-1 : 2 : 4-triazole* (I; R = Ph, *p*-MeO·C$_6$H$_4$, or *p*-C$_6$H$_4$Cl) were obtained. This cyclisation was also carried out with an alcoholic solution of sodium ethoxide (in moderate yield) but could not be effected with sulphuric or phosphoric acid (cf. the cyclisation of 1-benzoylthiosemicarbazides, Part II).

When benzhydrazide was treated with *S*-methyl-*NN*-pentamethyleneisothiourea, 5-piperidino-3-phenyl-1 : 2 : 4-triazole was formed directly. The intermediate benzamidoguanidine in this case appears to be cyclised during the isolation. The corresponding *p*-methoxyphenyl *compound* was obtained by using *p*-anishydrazide.

Experimental.

Reaction of 1-Benzoyl-S-methylisothiosemicarbazide with Ammonia.—The *S*-methylisothiosemicarbazide (4·2 g.) and alcohol (25 c.c.) containing dry ammonia gas (1·9 g.) were set aside for 12 hours and then refluxed for 4 hours. The solvent was evaporated under reduced pressure, and the residue triturated with *N*-sodium hydroxide (50 c.c.) and filtered. The insoluble residue, which was sulphur-free (2·3 g.; m. p. 236°), was crystallised from alcohol, giving colourless prisms (1·8 g.) of 2-amino-5-phenyl-1 : 3 : 4-oxadiazole, m. p. 243°, not depressed by an authentic specimen (Fehrenbach and Stolle, *J. pr. Chem.*, 1929, **122**, 289). The original filtrate was made just acid with acetic acid, and the precipitate collected (0·9 g.; m. p. 158—160°) (Found: S, 15·8%) and crystallised from water containing a little alcohol, giving colourless plates (0·6 g.) of 5-methylthio-3-phenyl-1 : 2 : 4-triazole, m. p. 162° (Part I, *loc. cit.*) (Found: C, 56·4; H, 4·3; S, 17·0. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7; S, 16·75%).

With *iso*propylamine (5·0 c.c.) in place of ammonia in the above experiment, the amino-oxadiazole (2·0 g.; m. p. 243°) and the methylthio-triazole (0·5 g.; m. p. 161°) were isolated. With diethylamine, triethylamine, or pyridine very similar results were obtained. The percentages of sulphur in the crude alkali-soluble fractions from these and the preceding experiment were 16·0, 16·7, 16·2, and 16·3 respectively.

Reaction of 1-Benzoyl-S-methylisothiosemicarbazide with Piperidine.—When the above experiment was repeated using piperidine (4·0 c.c.) in place of ammonia, the amino-oxadiazole (1·3 g.; m. p. 240°) was isolated as previously (Found: C, 59·6; H, 4·4. Calc. for $C_9H_7ON_3$: C, 59·6; H, 4·3%). The crude alkali-soluble fraction (1·4 g.; m. p. 135—140°) (Found: S, 7·2%) was rubbed in a mortar with N-hydrochloric acid (10 c.c.) for 1 minute and quickly filtered (the whole dissolved on rubbing with twice as much acid for 15 minutes). The residue (0·3 g.; m. p. 152—154°) (Found: S, 15·6%) was crystallised twice from aqueous alcohol giving colourless leaflets (0·2 g.) of the methylthio-triazole, m. p. 162° (Found: C, 56·5; H, 4·6%). The acid extract was precipitated with potassium hydrogen carbonate, the solid collected (1·0 g.; m. p. 170—180°) (Found: S, 0·2%) and crystallised from benzene–light petroleum (b. p. 60—80°) and then twice from benzene giving colourless needles (0·5 g.) of *5-piperidino-3-phenyl-1 : 2 : 4-triazole*, m. p. 196° (Found: C, 68·7; H, 6·8; N, 24·6. $C_{13}H_{15}N_4$ requires C, 68·4; H, 7·0; N, 24·6%).

Reaction of 1-p-Anisoyl-S-methylisothiosemicarbazide with Ammonia.—The *S*-methylisothiosemicarbazide (4·8 g.) and alcohol (25 c.c.) containing ammonia (1·8 g.) gave the amino-oxadiazole (Part III, *loc. cit.*), which crystallised from alcohol in large colourless needles (2·8 g.), m. p. 246—247°, and the methylthio-triazole (Part III, *loc. cit.*), which crystallised from aqueous alcohol in colourless leaflets (0·1 g.), m. p. 125° (Found: C, 54·2; H, 4·8. Calc. for $C_{10}H_{11}ON_3S$: C, 54·3; H, 5·0%). A similar result was obtained by using triethylamine (6·3 c.c.) in place of the ammonia, and in both cases the methylthio-triazole was formed in smaller amounts and was more difficult to purify compared with corresponding reactions with 1-benzoyl-*S*-methylisothiosemicarbazide.

Reaction of 1-p-Chlorobenzoyl-S-methylisothiosemicarbazide with Triethylamine.—The *S*-methylisothiosemicarbazide (4·9 g.), alcohol (30 c.c.), and triethylamine (6·3 c.c.) gave, as above, the amino-oxadiazole (Part III, *loc. cit.*) (2·1 g.) which crystallised from alcohol in colourless needles, m. p. 270°, and *5-methylthio-3-p-chlorophenyl-1 : 2 : 4-triazole* which crystallised from benzene in hard, refractive, colourless prisms (1·2 g.), m. p. 154° (Found: C, 48·2; H, 3·5; S, 14·2. $C_9H_6N_3SCl$ requires C, 47·9; H, 3·5; S, 14·2%). The same methylthio-triazole was obtained by shaking the triazole-thiol (0·7 g.) with N-sodium hydroxide (5 c.c.), methyl iodide (0·3 c.c.), and alcohol (1 c.c.). The precipitate, crystallised from benzene, gave colourless prisms (0·5 g.), m. p. 153°, not depressed by the compound as prepared above (Found: C, 48·0; H, 3·6%).

Attempt to cause 5-Methylthio-3-phenyl- or 5-Methoxy-3-p-methoxyphenyl-1 : 2 : 4-triazole to react with Sodium Ethoxide and Ammonia, respectively.—The methylthiotriazole (1·9 g.) was refluxed with a solution of sodium (0·8 g.) in alcohol (30 c.c.) for 24 hours and evaporated under reduced pressure. The residue was made just acid with acetic acid, and the solid collected and crystallised from aqueous alcohol, giving colourless leaflets (1·6 g.), m. p. 161—162°, not depressed by admixture with starting material.

The methoxy-triazole (Part III, *loc. cit.*) (0·5 g.) and alcohol (20 c.c.) containing ammonia (1·8 g.) were heated in a sealed tube at 110° for 18 hours. The residue left on evaporation of the solvent crystallised from aqueous alcohol in colourless needles (0·35 g.), m. p. 168—169°, not depressed by admixture with starting material.

Benzamidoguanidine (III; R = Ph).—(*a*) *S*-Methylisothiourea sulphate (13·9 g.) was added with stirring to ice-cold N-sodium hydroxide (100 c.c.), followed by benzhydrazide (13·5 g.). After storage for 3—4 days at room temperature (smaller yields were obtained after shorter times) the mixture was slowly heated to 50° and kept *for* 3 hours at this temperature. Purple-tinged crystals separated. The reaction vessel was cooled in a freezing mixture, a rapid stream of carbon dioxide passed in, and, after neutralisation, the solid was collected, washed with water, and dried (12·2 g.; m. p. 180—182°). *Benzamidoguanidine* was soluble in dilute acids but only sparingly soluble in sodium hydroxide solution, and crystallised from water (charcoal) in large colourless refractive prisms, m. p. 184° (decomp.) (Found: C, 54·2; H, 5·5; N, 31·9. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·6; N, 31·5%).

(*b*) Aminoguanidine hydrogen carbonate (6·0 g.) in dry pyridine (50 c.c.) was cooled to 0° and stirred whilst freshly distilled benzoyl chloride (6·0 c.c.) was added during 0·5 hour. After 12 hours' stirring at room temperature, the solvent was removed under reduced pressure, and the residue treated with water (50 c.c.) and made strongly alkaline with 10N-sodium hydroxide. The solid was collected (3·4 g.; m. p. 180—182°) and crystallised from water giving large colourless prisms, m. p. 185° (decomp.) (Found: C, 53·5; H, 5·7%). The alkaline filtrates were examined for amino-triazole but only benzoic acid (1·4 g.; m. p. 121°) was isolated.

The following were obtained in good yield by method (*a*): p-*anisamido*- (III; R = *p*-MeO·C_6H_4), colourless prisms which effloresce on drying (from water), m. p. 218—220° (Found: C, 52·0; H, 5·9. $C_9H_{12}O_2N_4$ requires C, 51·9; H, 5·8%), and p-*chlorobenzamido-guanidine* (III; R = *p*-C_6H_4Cl), colourless prisms (from aqueous alcohol), m. p. 194—196° (Found: C, 45·6; H, 4·3; N, 26·5. $C_8H_9ON_4Cl$ requires C, 45·2; H, 4·2; N, 26·4%). *p*-Chlorobenzhydrazide was much less soluble than the other hydrazides used and the reaction liquid was therefore diluted with an equal volume of alcohol and this solvent subsequently removed under reduced pressure at 50°.

5-Amino-3-phenyl-1 : 2 : 4-triazole (I; R = Ph).—(*a*) Benzamidoguanidine (5·0 g.) was heated in an oil-bath at 220°. Water was eliminated with decrepitation and after 5 minutes the residue was crystallised from water, giving colourless silky needles (3·8 g.), m. p. 186—187°, not depressed by a specimen prepared as described by Besack (*loc. cit.*) (Found: C, 59·8; H, 4·9. Calc. for $C_8H_8N_4$: C, 60·0; H, 5·0%). When benzamidoguanidine (1·8 g.) was added to sulphuric acid (98%; 20 c.c.) at 120° (with stirring), a sublimate of benzoic acid formed. After 0·5 hour's stirring, the mixture was poured on ice; the solid was collected (1·1 g.; m. p. 118°) and by crystallisation from water gave benzoic acid (0·6 g.; m. p. 120°). The acid filtrates contained no diazotisable amine. A similar result was obtained with phosphoric acid–phosphoric oxide.

(*b*) Benzamidoguanidine (1·8 g.) was refluxed with a solution of sodium (1·5 g.) in alcohol (100 c.c.) *for* 3 hours and the solvent removed under reduced pressure. Water (20 c.c.) was added, the small insoluble residue filtered off, and the filtrate made just acid with acetic acid. The precipitate (0·6 g.; m. p. 184°) was collected and crystallised from water giving colourless needles (0·4 g.), m. p. 186° (Found: C, 60·2; H, 5·2%).

The following were prepared by method (*a*): *5-amino*-3-p-*methoxyphenyl*- (I; R = *p*-MeO·C_6H_4), small colourless plates (from water), m. p. 224—226° (Found: C, 57·1; H, 5·3. $C_9H_{10}ON_4$ requires C, 56·8; H, 5·3%), and *5-amino*-3-p-*chlorophenyl*-1 : 2 : 4-*triazole* (I; R = *p*-C_6H_4Cl), large colourless needles (from aqueous alcohol), m. p. 227—229° (Found: C, 49·7; H, 3·9. $C_8H_7N_4Cl$ requires C, 49·4; H, 3·6%).

5-Piperidino-3-phenyl-1 : 2 : 4-triazole.—*NN*-Pentamethylenethiourea (6·0 g.) and water (10 c.c.) were shaken together and freshly distilled methyl sulphate (6·0 g.) added. On slight warming of the mixture, a vigorous reaction occurred. The clear solution was refluxed for 0·5 hour and evaporated under reduced pressure. The syrup (which could not be crystallised) was cooled in a freezing mixture, and N-sodium hydroxide added until the product was just alkaline to brilliant-yellow. Benzhydrazide (5·4 g.) was added, and after 3 days the reaction mixture was stirred and heated at 50° for 3 hours. The supernatant liquid was decanted from the sticky precipitate which was hardened by rubbing it with a little 10% acetic acid. The solid was collected (6·7 g.; m. p. 180°) and crystallised from aqueous alcohol, giving colourless needles (5·2 g.), m. p. 196—198°, not depressed by the compound prepared as above (Found: C, 68·5; H, 6·9%).

5-Piperidino-3-p-methoxyphenyl-1 : 2 : 4-triazole.—This *compound*, obtained as was the corresponding phenyl compound, crystallised from aqueous alcohol or benzene–light petroleum (b. p. 60—80°) in colourless plates, m. p. 206—208° (Found: C, 65·3; H, 6·9. $C_{14}H_{18}ON_4$ requires C, 65·1; H, 7·0%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED (RESEARCH LABORATORIES),
BLACKLEY, MANCHESTER, 9.

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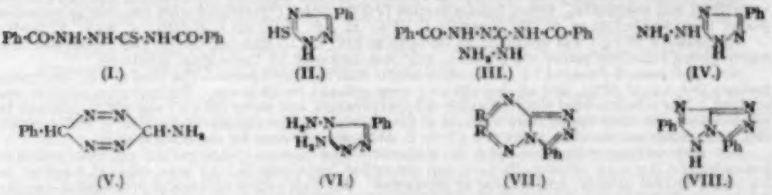
117. *Compounds related to Thiosemicarbazide. Part V. 4 : 5-Diamino-3-phenyl-4 : 1 : 2-triazole.*

By ERIC HOGGARTH.

1 : 4-Dibenzoylthiosemicarbazide reacts with hydrazine to give 3-phenyl-1 : 2 : 4-triazole-5-thiol, benzhydrazide, and a compound $C_8H_9N_5$, whose reactions indicate that it is 4 : 5-*diamino-3-phenyl-4 : 1 : 2-triazole*.

THE work recorded here arose out of the observation mentioned in an earlier report (Part I, *J.*, 1949, 1160) that the hydrazine salt of 1 : 4-dibenzoylthiosemicarbazide (I) was rapidly decomposed in boiling alcohol with evolution of hydrogen sulphide. It was to be expected that hydrazine, in view of its basic nature, would cause a cyclisation of the dibenzoyl compound

corresponding to that observed with 1-benzoylthiosemicarbazides (Part II, *J.*, 1949, 1163) and it was confirmed that with a solution of sodium in alcohol the expected cyclisation of (I) to 3-phenyl-1 : 2 : 4-triazole-5-thiol (II) (and benzoic acid) occurred. However the evolution of hydrogen sulphide with use of hydrazine indicated that, at least in part, interaction with elimination of the (potential) thiol grouping was taking place. When 1 : 4-dibenzoylthiosemicarbazide was refluxed with hydrazine and alcohol, a white crystalline sublimate formed. This sublimate was very unstable but a little of it, washed out with water, gave tests for hydrazine and the sulphide ion; it was probably a salt of hydrazine and hydrogen sulphide. In a stream of nitrogen no sublimate formed and absorption in acidified lead acetate solution showed that less than 50% of the theoretical amount of hydrogen sulphide (supposing complete elimination) was actually evolved. The residual solution was shown to contain the triazole-thiol (II), benzhydrazide, and a *compound* $C_8H_9N_5$, the formula of which is obtained by replacement of the thiol group by hydrazine and elimination of the elements of benzoic acid. It was shown that



(I.) (II.) (III.) (IV.)

(V.) (VI.) (VII.) (VIII.)

the triazolethiol was completely inert towards hydrazine under the reaction conditions and it seemed therefore that this new compound arose by a cyclisation of the (hypothetical) dibenzoyldiaminoguanidine (III). Of the three possible structures which must be considered (IV, V, and VI) the first two may be eliminated.

5-Hydrazino-3-phenyl-1 : 2 : 4-triazole (IV) was prepared (but not isolated) by Manchot (*Ber.*, 1910, **43**, 1312) and shown to form a well-defined monobenzylidene and related derivatives. The compound $C_8H_9N_5$ reacted with benzaldehyde or *p*-methoxybenzaldehyde in the presence of a little sodium hydroxide (but not in its absence) to give *dibenzylidene* and *di*-p-*methoxybenzylidene* derivatives having melting points quite different from those of the benzylidene derivatives described by Manchot. Further evidence for the 4 : 5-diamino-4 : 1 : 2-triazole structure was found in the ready condensation with α-diketones (benzil, diacetyl) to give 1 : 2 : 4 : 7 : 9-*penta-azaindenes* (VII; R = Ph or Me). Although these reactions seem conclusive in favour of structure (VI) it is known that dihydro-1 : 2 : 4 : 5-tetrazines are readily isomerised to *N*-aminotriazole derivatives. Thus Curtius, Darapsky, and Müller (*Ber.*, 1907, **40**, 815) found that dihydro-1 : 2 : 4 : 5-tetrazine itself gave 4-amino-4 : 1 : 2-triazole on fusion. It was possible therefore, that the compound $C_8H_9N_5$ had the dihydrotetrazine structure (V) and was giving derivatives of (VI) under the influence of alkaline catalysts. This possibility was disproved by showing that the compound was unchanged by fusion and recovered from the dibenzylidene compounds, mentioned above, by hydrolysis. Dihydrotetrazines in general are very readily oxidised to the corresponding tetrazines, many of which have an intense purple colour. The compound $C_8H_9N_5$ did not develop such a colour with oxidising agents but when first isolated was purple, the intensity varying from experiment to experiment. This colour, which may be ascribed to the oxidation of a trace of dihydrotetrazine contaminant, was lost on crystallisation.

Under mild conditions, 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole gave a *monobenzoyl* compound from which, by acid hydrolysis, the parent diamine could be recovered. By further reaction of the monobenzoyl derivative, or of the diamine with excess of benzoyl chloride, a *substance* $C_{22}H_{15}ON_5$ was obtained, corresponding to a dibenzoyl compound less the elements of water. On hydrolysis of this a *compound* $C_{15}H_{11}N_5$ was obtained which probably has the triazolotriazole structure (VIII).

Experimental.

Reaction of 1 : 4-*Dibenzoylthiosemicarbazide with Sodium Ethoxide Solution.*—The dibenzoyl compound (3·8 g.) was refluxed with a solution of sodium (1·2 g.) in alcohol (50 c.c.) until the copious yellow precipitate (the sodium salt of the dibenzoyl compound) had disappeared (*ca.* 16 hours). After cooling, the precipitated sodium benzoate (1·8 g.) was collected and dissolved in water, and the benzoic acid precipitated with acid (1·2 g.; m. p. 119—120°). The initial filtrate was evaporated under reduced pressure, and the residue dissolved in water (30 c.c.), filtered (charcoal), and precipitated with hydrochloric acid.

The 3-phenyl-1 : 2 : 4-triazole-5-thiol (2·0 g.; m. p. 255—256°) was crystallised from water, giving colourless needles (1·6 g.), m. p. and mixed m. p. 256—257° (Part I, *loc. cit.*) (Found: C, 54·3; H, 4·0. Calc. for $C_8H_7N_3S$: C, 54·2; H, 4·0%).

Reaction of 1 : 4-*Dibenzoylthiosemicarbazide with Hydrazine.*—A mixture of the dibenzoyl compound (6·0 g.), alcohol (50 c.c.), and hydrazine hydrate (8·0 c.c. of 50%) was refluxed in a stream of nitrogen until evolution of hydrogen sulphide ceased (8—9 hours). The effluent gas was washed in acidified lead acetate solution, and the lead sulphide collected in a Gooch crucible and dried at 110° (2·2 g.). The residual solution was evaporated under reduced pressure, the residue dissolved in water (50 c.c.), and hydrochloric acid was added, with good cooling, until the mixture was just acid to Congo-red paper. The precipitate (2·1 g.; m. p. 235—240°) was crystallised twice from water, giving colourless needles (0·7 g.) of 3-phenyl-1 : 2 : 4-triazole-5-thiol, m. p. 256—257° (Found: C, 54·5; H, 4·3%). The acid filtrates were evaporated under reduced pressure, the residue was cooled strongly, and 40% potassium hydroxide solution (10 c.c.) was added. The pink-tinged solid was collected (0·4 g.), washed with a little ice-water, and crystallised from water or alcohol, giving large colourless plates of 4 : 5-*diamino*-3-*phenyl*-4 : 1 : 2-*triazole* (0·25 g.), m. p. 224° (Found: C, 55·1; H, 5·3; N, 39·6. $C_8H_9N_5$ requires C, 54·9; H, 5·1; N, 40·0%). The alkaline filtrates were cooled, made just acid with 10% acetic acid, and evaporated under reduced pressure. The dry residue was extracted with chloroform, and the extracts were dried and evaporated, giving benzhydrazide (2·6 g.) which crystallised from benzene as colourless plates, m. p. and mixed m. p. 113° (Found: C, 61·9; H, 5·9. Calc. for $C_7H_8ON_2$: C, 61·8; H, 5·9%).

The diamine (0·5 g.) was melted in an oil-bath at 230° for 15 minutes, cooled, and crystallised from water, giving colourless plates (0·3 g.), m. p. 224°, not depressed by the original substance.

Attempt to cause 3-*Phenyl*-1 : 2 : 4-*triazole*-5-*thiol to react with Hydrazine.*—The thiol (1·8 g.), hydrazine hydrate (5·0 c.c. of 50%), and alcohol (50 c.c.) were refluxed for 36 hours. No hydrogen sulphide was evolved. The solvents were removed under reduced pressure, and water (25 c.c.) was added, followed by hydrochloric acid until the mixture was acid to Congo-red. The precipitate (1·5 g.; m. p. 258°) crystallised from water as colourless plates (1·0 g.), m. p. 258°, not depressed by the original thiol.

4 : 5-*Bisbenzylideneamino*-3-*phenyl*-1 : 2 : 4-*triazole.*—The diamino-compound (1·0 g.), freshly distilled benzaldehyde (1·0 c.c.), alcohol (20 c.c.), and potassium hydroxide (0·1 g.) were refluxed together for 0·5 hours, filtered quickly, and allowed to crystallise. The pale yellow crystals of *bisbenzylideneamino*-compound (1·0 g.) were collected and recrystallised from alcohol, giving yellow needles (0·6 g.), m. p. 202—203° (Found: C, 75·1; H, 5·0; N, 20·3. $C_{22}H_{17}N_5$ requires C, 75·2; H, 4·8; N, 20·0%). There was no precipitate when the same mixture but without the potassium hydroxide was boiled for 24 hours. This compound (0·3 g.) was boiled for 1 minute with concentrated hydrochloric acid (5 c.c.), and excess of acid evaporated in a dish. N-Hydrochloric acid (5 c.c.) was added, the oily drops of benzaldehyde were removed with ether, and the residual aqueous solution was clarified (charcoal) and treated with 40% potassium hydroxide solution. The pearly leaflets precipitated were collected, washed with ice-water, and crystallised from water, giving colourless plates (0·1 g.), m. p. 225°, not depressed by admixture with the diamine (Found: C, 54·5; H, 5·1%).

By use of *p*-methoxybenzaldehyde in place of benzaldehyde, the corresponding 4 : 5-*bis*-p-*methoxybenzylideneamino*-*triazole* was obtained as yellow clumps of needles (1·0 g.), m. p. 165° (from alcohol) (Found: C, 69·9; H, 4·6; N, 17·1. $C_{24}H_{21}O_2N_5$ requires C, 70·1; H, 5·1; N, 17·0%). Hydrolysis of this compound with acid gave *p*-methoxybenzaldehyde and the original diamine, m. p. and mixed m. p. 225°.

3 : 5 : 6-*Triphenyl*-1 : 2 : 4 : 7 : 9-*penta-azaindene* (VII; R = Ph).—The diamine (1·0 g.), benzil (1·2 g.), and alcohol (20 c.c.) were refluxed for 12 hours and cooled, whereupon benzil (1·0 g.) (only) separated. The original mixture, but with the addition of sodium hydroxide (0·05 g.), became intensely yellow on heating, and crystals separated. After 1 hour, the mixture was cooled, and the solid collected and crystallised from 2-ethoxyethanol giving the *penta-azaindene* as square, deep-yellow plates (1·0 g.), m. p. 250° (Found: C, 75·5; H, 4·5; N, 20·1. $C_{20}H_{13}N_5$ requires C, 75·6; H, 4·3; N, 20·1%).

3-*Phenyl*-5 : 6-*dimethyl*-1 : 2 : 4 : 7 : 9-*penta-azaindene* (VII; R = Me).—The above experiment was repeated with diacetyl (1·0 c.c.) in place of benzil, giving a yellow *product* which crystallised from aqueous diethylformamide in long deep-yellow needles (0·6 g.), m. p. 203° (Found: C, 64·2; H, 4·8; N, 31·1. $C_{15}H_{11}N_5$ requires C, 64·0; H, 4·9; N, 31·1%).

Action of Benzoyl Chloride on 4 : 5-*Diamino*-3-*phenyl*-4 : 1 : 2-*triazole.*—The diamine (1·8 g.) was dissolved in dry pyridine (75 c.c.) at 80° and a solution of benzoyl chloride (1·5 g.) in dry pyridine (10 c.c.) added with shaking. After 10 minutes, the pyridine was evaporated under reduced pressure, the residue treated with water (100 c.c.), and the solid collected, washed with water, and dried at 100° (3·0 g.; m. p. 258°). From alcohol, in which it is not very soluble, this *benzoyl* derivative crystallised in colourless leaflets, m. p. 264—266° (Found: C, 64·1; H, 4·9; N, 25·2. $C_{15}H_{10}ON_5$ requires C, 64·5; H, 4·7; N, 25·1%). The same compound was obtained by rubbing the diamine (0·5 g.) with benzoyl chloride (0·5 g.), whereupon a vigorous reaction took place. Pyridine (1 c.c.) was added, the mixture cautiously warmed to effect dissolution, and ice and water (20 g.) were added. The solid was collected and crystallised as above, giving colourless leaflets (0·4 g.), m. p. 266°. This compound (0·75 g.) was refluxed with 2-ethoxyethanol (15 c.c.) and concentrated hydrochloric acid (2·5 c.c.) for 0·5 hour and the solvent removed under reduced pressure. The residue was treated with N-sodium hydroxide (5 c.c.), and the solid collected and crystallised from water, giving colourless plates (0·25 g.), m. p. 224°, not depressed on admixture with the diamine. The benzoyl compound was stable to boiling N-sodium hydroxide, giving, on cooling, a crystalline sodium salt from which the original benzoyl compound was recovered by dissolution in N-hydrochloric acid and neutralisation with potassium hydrogen carbonate.

The above benzoyl compound (0·5 g.), benzoyl chloride (1 c.c.), and dry pyridine (10 c.c.) were refluxed for 12 hours. Water (15 c.c.) was added (too much water precipitated a tar), and the solid collected and washed, until nearly colourless, with alcohol. From alcohol the *substance* crystallised in colourless needles (0·4 g.), m. p. 196° (Found: C, 72·2; H, 4·0. $C_{22}H_{15}ON_5$ requires C, 72·3; H, 4·1%). The same substance was obtained from the original diamine (0·5 g.), benzoyl chloride (1·0 c.c.), and pyridine (10 c.c.), and crystallised from alcohol in colourless needles (0·45 g.), m. p. 196—198° (Found:

C, 72·4; H, 4·2%). This substance (2·8 g.), concentrated hydrochloric acid (5·0 c.c.), and 2-ethoxyethanol (50 c.c.) were refluxed for 3 hours. The solvent was removed under reduced pressure, and the residue dissolved in water (100 c.c.) and neutralised with potassium hydrogen carbonate. The solid was collected (2·0 g.; m. p. 230—235°) and crystallised from alcohol, giving (?) 5 : 5'-*diphenyl*-2 : 3-*dihydro*-4' : 1' : 2'-*triazolo*(4' : 3'-2 : 3)-1 : 2 : 4-*triazole* (VIII) as colourless felted needles (1·5 g.), m. p. 257° (Found : C, 68·6; H, 4·5; N, 27·1. $C_{15}H_{11}N_5$ requires C, 69·0; H, 4·2; N, 26·8%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED (RESEARCH LABORATORIES), BLACKLEY, MANCHESTER, 9.

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118. *Covalency, Co-ordination, and Chelation. Part III.*

By W. J. LILE and R. C. MENZIES.

The changes in covalency on passing from quadrivalent platinum through tervalent gold to bivalent mercury are discussed with reference to the derived organometallic pseudo-atoms and ions and the additive compounds of some of the latter with amines. The further changes on proceeding to tervalent thallium, quadrivalent lead, and bismuth are outlined.

Similar changes passing down sub-groups IIIb, IVb, and Vb to the same metals are also discussed. A few illustrative experiments are described.

THE co-ordination numbers (C.N.) characteristic of the elements from Os (76) to Po (84) in their highest valency states are now well established in inorganic compounds, and pass from a maximum of 8 at osmium (as in OsF_8) through 6 (IrF_6, $[PtCl_6]''$) to a minimum of 4 in gold, *e.g.*, $(Au\ en_2)Br_3$, and in mercury, *e.g.*, $[HgI_4]''$. Beyond this point the maximum C.N. remains at 6 for the next three elements, as shown by the thalli-, plumbi-, and bismuthi-chloride ions, rising finally to 8 again in the acetylacetone derivative of polonium (Servigne, *Compt. rend.*, 1933, **196**, 264).

In lower-valency states a minimum of 2 is found in the same place, as illustrated by $[Au,2CS(NH_2)_2]Cl$, and by the fact that mercurous chloride does not add pyridine, but is decomposed by it, giving mercury and the pyridine complex of mercuric chloride (Lang, *Ber.*, 1888, **21**, 1578).

Definite organo-metallic compounds of osmium and iridium have not yet been described, although Lichtenwalter (Thesis, Iowa State College, 1939, pp. 59, 60) obtained small amounts of amorphous material containing carbon and metal when the trichlorides were treated with phenylmagnesium bromide.

In all its compounds, inorganic, organic and complex, quadrivalent platinum has a co-ordination number of 6, the bonds being directed to the corners of an octahedron (Werner, *Vierteljahrschrift Naturf. Ges., Zurich*, 1917, **62**, 553). Where one atom of quadrivalent platinum appears to be surrounded by less than six other atoms or groups, as in the trimethylplatinum halides (Part I, *J.*, 1933, 1292), association always occurs. Again trimethylplatinum acetylacetone, the single formula for which suggests a co-ordination number of 5 for the metal, was shown (*J.*, 1928, 565) to be bimolecular in benzene, as were later the ethyl acetoacetate and dipropionylmethane derivatives (*J.*, 1933, 21). Another example of the same behaviour has now been provided by the new monopyridine derivative of trimethylplatinic iodide (Gibson, Ewens, and Foss, *Nature*, 1948, **162**, 693), which is also bimolecular in benzene.

The 6-co-valency of quadrivalent platinum, in three dimensions, and the stability of its methyl compounds and of its co-ordination compounds with β-diketones, with ammonia, and with organic amines, are all well established, both organic and organometallic compounds being built on the same plan.

The work of Gibson and his school on the organic derivatives of gold, summarised in his Presidential Address to the British Association (Cambridge, 1938), has established that tervalent gold is 4-co-ordinate in its inorganic, organic, and complex compounds, the metal lying at the centre of a square and the other atoms or groups at the four corners. Brain and Gibson, in particular (*J.*, 1939, 765), attempted, but failed, to prepare a stable compound containing 5-co-ordinate auric gold. All that has been said about quadrivalent platinum and the octahedron may, with equal truth, be said about tervalent gold and the square. Moreover, within the framework of the above, both gold and platinum in both their inorganic and organometallic compounds form well-defined and stable compounds with β-diketones and with amines, the stability of their derivatives with ethylenediamine having been again demonstrated by Gilman and Wood's preparation (*J. Amer. Chem. Soc.*, 1948, **70**, 550) of bistrimethylgold–ethylenediamine, decomposing at 94—98°, while their trimethylgold from which it is derived decomposes below −40°.

The organometallic compounds of mercury (*e.g.*, diphenylmercury, alkylmercury halides) do not form stable compounds with either β-diketones or amines, although they are soluble in pyridine and ethylenediamine, from which they are recovered unchanged. Evidence of combination is, however, provided by Maynard and Howard's observation (*J.*, 1923, **123**, 963) that the conductivity of an aqueous solution of methylmercury acetate was increased by the addition of pyridine. This suggests co-ordinate combination of the pyridine and the methylmercury group and extrusion of the acid radical as an ion, leaving the C.N. of mercury unchanged. There is yet no evidence that mercury in its organometallic derivatives ever has a higher covalency than 2.

Both valency and co-ordination number of organometallic compounds thus decrease on approaching mercury, and on passing beyond it a new and different structure appears, of which the strongly alkaline nature of the thallous and dialkylthallium hydroxides is an early indication, as is the reactivity of the third alkyl group in the trialkylthallium compounds. These changes resemble those found on passing towards and beyond an inert gas (cf. Berry and Lowry, *J.*, 1928, 1765; Hartmann, *Z. Naturforsch.*, 1947, **2**, *a*, 489). The mercury atom and the thallous ion are related as are argon and potassium, and the mercury dialkyls to the dialkylthallium ions as methane to the ammonium ion.

The alkylmercury halides and the dialkylthallium ions differ from the trialkyl derivatives of platinum and from the dialkyl derivatives of gold, but resemble each other, in not forming stable compounds with pyridine or with ethylenediamine; both, however, are soluble in these solvents. In the compounds of platinum and gold, the forces attaching these addenda to the molecule are of a higher order than those between solvent and solute. In the compounds of mercury, thallium, and lead, they are of the same order, organometallic lead complexes with pyridine and ammonia being unstable; thus diphenyl-lead dibromide forms a compound with four molecules of pyridine which is described as being stable in a pyridine atmosphere, and also with two molecules of ammonia, which can be removed by the passage of air (Pfeiffer, Truskier, and Disselkamp, *Ber.*, 1916, **49**, 2448). This is a contrast to the behaviour of the dipyridyl derivative of trimethylplatinum iodide, which, as described in Part II (Lile and Menzies, *J.*, 1949, 1168), is unattacked by boiling with dilute acetic or hydrochloric acid, 2N-ammonia, or sodium hydroxide. This decrease of the power of attachment is general. Tetramethylplatinum, for instance, is unaffected by iodine, but the tetra-alkyl derivatives of lead are readily decomposed by it. The trialkylbismuths are spontaneously inflammable in air.

Tetramethylplatinum, again, has no melting point, and is tetrameric in the solid state. Diphenylmercury, trimethylthallium, tetraethyl-lead, and triphenylbismuth are all unimolecular (Ghira, *Gazzetta*, 1894, **24**, 312; Abbott, Doctoral Thesis, Iowa State College, 1942, p. 28; Menzies and Overton, *J.*, 1933, 1292; Challenger and Goddard, *J.*, 1920, **117**, 771; see also p. 620).

Although Challenger and Parker (*J.*, 1931, 1462) and Challenger and Richards (*J.*, 1934, 409) have prepared pyridine derivatives of phenylthallium dihalides, and Molnikoff and Gratschewa (*J. Russ. Phys. Chem. Soc.*, 1935, **67**, 1768) those of ethylthallium dibromide, it is shown below that not only methylmercury iodide, but also dimethyl- and diethyl-thallium halides are recovered unchanged on adding water to their solutions in pyridine or ethylenediamine. It is also shown that diphenylmercury, triphenyl-antimony and -bismuth, and tetraphenyl-lead separate unchanged from their solutions in organic solvents containing also ethylenediamine, *i.e.*, under conditions which convert the trimethylplatinum and dialkylgold compounds into stable complexes. If thallium resembles mercury and differs from platinum and gold in not forming stable compounds with organic amines in its dialkyl and diaryl derivatives, it resembles them in forming the stable dialkylthallium derivatives of β-diketones (Menzies, Sidgwick, Cutcliffe, and Fox, *J.*, 1928, 1288). Here, as often, carrying a charge helps both initial attachment and subsequent co-ordination, the familar arrow being electrically supported near the target. These stable, volatile compounds display both the stable combination leading to definite and reproducible composition, and the less stable form involving forces of the same order as those involved in solution. Their association in benzene depends on the concentration (*J.*, 1932, 2734). The corresponding platinum compounds display double molecular weights in benzene at all concentrations.

The elements and groups attached to the heavy metals preceding mercury are more firmly held and in more definite positions than those following it, around which also the form taken by co-ordination is frequently different. 4-Covalent quadrivalent lead, for example is tetrahedral, but optically active lead compounds have not yet been described, racemisation after their attempted preparation possibly taking place on the lines suggested by Garner (*Proc.*,

1912, **28**, 67). This loosening becomes apparent on approaching thallium, lead, and bismuth, both from above and from the left. Practical applications of this have been made by Challenger and Ridgeway and by Goddard and Goddard (*J.*, 1922, **121**, 104, 256) who used triphenylbismuth as a phenylating agent for the earlier members of Group V, and for mercuric and thallic chlorides.

Experimental.

Action of Ethylenediamine and Pyridine on Methylmercury Iodide.—The ethylenediamine used for this and for the dialkylthallium halides was part of a consignment of 38½ lb. purchased from the Beresworth Laboratories of Framlingham, Mass., early in 1937 and kept since in stoppered bottles; in 1949 it had become light brown and had taken up a little water. It was kept for a few days over potassium hydroxide and then distilled twice from sodium wire. It then boiled at 116—117°/740 mm. and titration by *N*-sulphuric acid, with methyl-red as indicator, showed a purity of 99·7%. The pyridine used was distilled from a good commercial sample, the fraction of b. p. 114°/745 mm. being used. The methylmercury iodide was the same sample as that used in Part I; it melted at 142—145°, and after drying (P_2O_5), at 145—146°. A sample was dissolved in cold pyridine and reprecipitated by addition of water; after separation and drying (P_2O_5) it melted at 143—144°. A sample was then dissolved in the above purified ethylenediamine, the solution boiled, and water added; a little solid separated out, m. p., after drying over sulphuric acid, 142°. On adding hydrochloric acid to the filtrate, much more solid was again precipitated; m. p. (P_2O_5) 145°, mixed m. p. with original methylmercury iodide 145—146°.

Precipitation on adding water is apparently much more complete with solutions of methylmercury iodide in pyridine than with those in ethylenediamine.

Action of Ethylenediamine on Dialkyl- and Diaryl-thallium Halides.—In most cases mixed m. p.s of the substances before and after recovery afford sufficient evidence of identity, but since the dimethyl- and diethyl-thallium halides have no m. p.s, another means of identification is supplied by the unique and unexplained patterns formed by these substances on the surfaces of drops of their hot solutions cooled on a microscope slide (see *Nature*, 1931, **128**, 907). All these halides are very soluble in anhydrous ethylenediamine, but in contrast to the behaviour of trimethylplatinic iodide they are reprecipitated by water, and even if the halides are boiled with the amine, on subsequent addition of water, the above patterns can be obtained just as if the amine had not been used, formation being occasionally facilitated in both cases by addition of a little of the corresponding alkali halide.

Diphenylthallium bromide does not form these patterns, but analysis of a sample dissolved in anhydrous ethylenediamine and then left until dry over sulphuric acid indicated that, apart from a little adhering ethylenediamine, it was recovered unchanged (Found: C, 33·9; H, 2·4; Br, 16·7; N, 0·68. Calc. for $C_{12}H_{10}TlBr$: C, 32·8; H, 2·3; Br, 18·24; N, 0%. Calc. for $C_{12}H_{10}TlBr,NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$: N, 5·6%). The high carbon and low bromine figures are probably due to the presence of diphenylthallium chloride.

Pyridine has so long been used for recrystallisation of dialkyl- and diaryl-thallium halides that further evidence of their separating unchanged is unnecessary.

Action of Ethylenediamine on Triphenylantimony, Triphenylbismuth, Diphenylmercury, and Tetraphenyl-lead.—Triphenylantimony (m. p. 51°) was prepared by the action of phenylmagnesium bromide on freshly distilled antimony trichloride, b. p. 216—217° (Pfeiffer and Heller, *Ber.*, 1904, **37**, 4621). The antimony was determined by heating with nitric and sulphuric acids, reduction by sulphur dioxide, boiling off excess of the latter, and iodometric titration (Found: Sb, 34·7, 34·5. Calc. for $C_{18}H_{15}Sb$: Sb, 34·5%). Triphenylbismuth (m. p. 78·5°) was similarly prepared from phenylmagnesium bromide and bismuth trichloride (Pfeiffer and Pietsch, *ibid.*, p. 4622). Tetraphenyl- and triphenyl-lead were prepared together by the action of phenylmagnesium bromide on lead chloride and separated by acetone, in which the latter is easily soluble, followed by recrystallisation from chloroform [Found, for triphenyl-lead: Pb, 47·5 (as sulphate). Calc. for $C_{18}H_{15}Pb$: Pb, 47·2%. Found, for tetraphenyl-lead: Pb, 39·1. Calc. for $C_{24}H_{20}Pb$: Pb, 40·2%].

Triphenylantimony, insoluble in hot aqueous ethylenediamine, dissolves readily in the anhydrous solvent. This solution, after addition of alcohol, was evaporated until solid separated; after recrystallisation from alcohol, this melted at 49—50° (mixed m. p. with triphenylantimony, 49—51°).

Action of Ethylenediamine on Other Phenyl–Metal Derivatives.—The compounds were dissolved in benzene, ethylenediamine added, and the solution evaporated to give a solid, as follows:

Compound.	Original.	M. p.	Product.	M. p.	Mixed m. p.
$Pb(C_6H_5)_4$	White needles	224°	White crystals	219°	221°
$Bi(C_6H_5)_3$	White needles	77—78	White needles	76	77—78
$Hg(C_6H_5)_2$	White needles	122—124	Rhombic plates	122—123	122—123

Ethylenediamine therefore does not appear to attack phenyl-metal derivatives in the absence of an acid group.

Triphenylantimony dibromide was made (13 g., 90% yield) by mixing solutions of triphenylantimony (10 g.) and a slight excess of bromine in light petroleum, filtration, and recrystallisation from the same solvent (charcoal); m. p. 214—215° (Michaelis and Reese, *Annalen*, 1886, **233**, 48, gave m. p. 216°) (Found: Sb, 24·3. Calc. for $C_{18}H_{15}SbBr_2$: Sb, 23·8%). The high m. p. and consequent stability are in contrast with the properties of triphenylbismuth dibromide, which decomposes in boiling benzene.

Triphenylantimony dichloride was prepared similarly as long colourless needles (up to 8 cm. long); m. p. 143° (Found: Sb, 30·2, 29·9, 29·9. Calc. for $C_{18}H_{15}SbCl_2$: Sb, 28·8%).

Triphenylantimony sulphide was prepared (theoretical yield) by passing hydrogen sulphide into a

cooled alcoholic solution of triphenylantimony dibromide saturated with ammonia; m. p. 112° (Kaufmann, *loc. cit.*, p. 2765, gives m. p. 119—120°) (Found: Sb, 31·4. Calc. for $C_{18}H_{15}SbS$: Sb, 31·6%). The compound is apparently more soluble in alcohol than stated by Kaufmann, 3·7 g. dissolving readily in 20 c.c. of boiling alcohol. It crystallises in needles on cooling. The alcoholic mother-liquors, on cooling, deposit large, colourless, rhombic plates, m. p. 51°, evidently of triphenylantimony re-formed by decomposition of the sulphide. Similarly, a benzene–hexane solution deposits crystal of rhombic sulphur on standing for some days.

The similar treatment (Michaelis and Polis, *Ber.*, 1887, **20**, 57) of triphenylbismuth dichloride or dibromide leads to formation of triphenyl bismuth, ammonium halide, and sulphur.

The molecular weights of three of the above compounds were determined cryoscopically in benzene, with the following results:

Compound.	Weight (g.).	Weight of benzene (g.).	Δ.	*M*, found.	*M*, calc.
$Sb(C_6H_5)_3$	0·7179	17·28	0·619°	348·4	352·9
	0·9894	16·16	0·893	351·1	
	1·7445	16·16	1·583	349·2	
$Sb(C_6H_5)_3Br_2$	0·9707	18·24	0·508	536·4	512·7
	1·4344	18·24	0·758	531·1	
	1·9257	18·24	1·019	530·8	
$Sb(C_6H_5)_3S$	0·2647	15·08	0·196	458·5	385
	0·4797	15·08	0·380	428·7 *	

* During this determination, some decomposition occurred, and the solution became milky.

Triphenylbismuth and its Dichloride.—By passing chlorine through a light petroleum solution of triphenylbismuth, the corresponding dichloride was obtained; m. p. 141° (Michaelis and Polis, *ibid.*, p. 56). Molecular weights were determined cryoscopically in benzene (the constant used was 51·15):

Compound.	Weight (g.).	Weight of benzene (g.).	Δ.	*M*, found.	*M*, calc.
$Bi(C_6H_5)_3$	0·5412	17·49	0·348°	455·3	440·1
	0·9334	17·49	0·602	453·9	
	1·6251	17·49	1·042	456·4	
$Bi(C_6H_5)_2Cl_3$	0·3756	16·63	0·238	485·9	511
	0·5956	16·63	0·379	484·0	
	0·7701	16·63	0·486	488·0	

Challenger and Goddard (*J.*, 1920, **117**, 771) found 427 for the molecular weight of triphenylbismuth in benzene, but as their observed depression was only 0·153°, they were obviously using a more dilute solution. Their figure 498·5 for the molecular weight of the dichloride was calculated from an observed depression of 0·47° and agrees well enough with our value.

Action of Ethylenediamine on Triphenylantimony Dichloride.—The dichloride (4 g.) was dissolved in ether, and ethylenediamine (0·6 c.c., 1 equiv.) added. A white precipitate was produced. This was filtered off, washed with alcohol, and dried, forming minute white crystals, m. p. 206° (decomp. at 235°). The compound was analysed without further purification. The figures show the presence of nitrogen but do not indicate any definite compound (Found: Sb, 23·7; C, 44·4; H, 5·3; N, 6·6. Calc. for $C_{18}H_{15}SbCl_2,NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$: Sb, 24·2; C, 49·6; H, 4·8; N, 5·8%).

Triphenylantimony dichloride was stirred with aqueous ethylenediamine. The solid became curdy. It was filtered off and dried in a vacuum desiccator, but did not contain Cl or N; m. p. 208°; mixed m. p. with the corresponding compound from the dibromide, 210°. It is therefore presumably triphenylantimony dihydroxide.

Action of Ethylenediamine on Triphenylantimony Dibromide.—This dibromide is only slightly soluble in anhydrous ethylenediamine. Addition of ethylenediamine to a solution of the dibromide in alcohol–ether or in benzene gives a white precipitate. This white solid is very deliquescent, and extremely soluble in water, from which it cannot be crystallised; it does not melt below 280°. Heated in a test-tube, it leaves only a slight residue of carbon. It contains bromine and nitrogen, but less than 2% of antimony. With copper sulphate solution it gives the deep blue colour characteristic of ethylenediamine–copper complexes. It would seem, therefore, to be ethylenediaminium dibromide.

Triphenylantimony dibromide (4 g.) was suspended in water, and a few c.c. of ethylenediamine were added. The solid changed in appearance, forming hard cakes. These were broken up, filtered off, washed, and dried, giving a white solid, m. p. 210°, which did not contain either nitrogen or bromine (Found: Sb, 31·8, 33·3. Calc. for $C_{18}H_{15}Sb(OH)_2$: Sb, 31·5%. Calc. for $C_{18}H_{15}SbO$: Sb, 33·1%); the dihydroxide has m. p. 212°.

Tetraphenyl-lead was heated under reflux with glacial acetic acid, and the diacetate formed was crystallised from dilute acetic acid; it was then dissolved in dilute acetic acid, and hydrogen sulphide passed through the cooled solution. The grey curdy precipitate was separated, extracted with benzene, and the solution crystallised, forming pale yellow prisms, m. p. 130° (decomp. above 90°) (Found: Pb (as sulphate), 51·05; S, 7·94. Calc. for $C_{18}H_{20}PbS$: Pb, 52·69; S, 8·16%). The sulphur was determined as barium sulphate after fusion with potassium hydroxide and nitrate.

Molecular weights, determined cryoscopically in benzene, were as follows:

Compound.	Weight (g.).	Weight of benzene (g.).	Δ.	*M*, found.	*M*, calc.
$Pb(C_6H_5)_3$	0·2260	15·30	0·097°	780	438
	0·4757	15·30	0·201	792	
$Pb(C_6H_5)_2S$	0·5540	23·08	0·120	1006	393
	0·5540	15·90	0·172	1019	

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UNIVERSITIES OF BRISTOL AND EDINBURGH.
MID-ESSEX TECHNICAL COLLEGE, CHELMSFORD.

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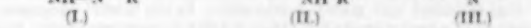
119. *The Fischer Indole Synthesis. Part III. The Cyclisation of the Phenylhydrazones of Some 2-Substituted* cyclo*Hexanones.*

By K. H. PAUSACKER.

Cyclisation of the phenylhydrazones of a number of 2-substituted *cyclo*hexanones has been effected using both dilute sulphuric acid and glacial acetic acid. Whereas sulphuric acid favoured the formation of the neutral tetrahydrocarbazole, the basic tetrahydrocarbazolenine was the principal product formed when glacial acetic acid was used. A detailed investigation of the action of a large number of cyclising agents on the phenylhydrazone of 2-methyl*cyclo*hexanone has also been made. Certain of the tetrahydrocarbazoles obtained have been dehydrogenated by using palladised charcoal.

It is well known that the phenylhydrazones of 2-substituted *cyclo*hexanones (I) may be cyclised to form both a neutral tetrahydrocarbazole (II) and a basic tetrahydrocarbazolenine (III).



(I.) (II.) (III.)

Pausacker and Schubert (*J.*, 1949, 1384) found that when R = Me the ratio $\frac{\text{yield of (II)}}{\text{yield of (III)}}$ (hereafter termed *a*) was 2·1 when dilute sulphuric acid was used, whereas Lions (*J. Proc. Roy. Soc. N.S.W.*, 1938, **71**, 206) found that, when R = Et, *a* was 0·13 with glacial acetic acid as the cyclising agent. As this comparison is made on two different substances, it was decided to study the influence of these two cyclising agents on compounds of type (I). The results are summarised in Table I.

TABLE I.

	Dilute sulphuric acid.			Glacial acetic acid.		
R.	Yield of (II), %.	Yield of (III), %.	*a*.	Yield of (II), %.	Yield of (III), %.	*a*.
Methyl	45	21	2·1	6 *	61	0·10
Ethyl	44	28	1·6	13	76	0·17
*iso*Propyl	44	18	2·4	16	70	0·23
*cyclo*Hexyl	29	17	1·7	9	79	0·12
Phenyl	54	19	2·8	27	69	0·39

* Appreciable amounts of *N*-acetylphenylhydrazine were also isolated.

It is thus seen that in every case dilute sulphuric acid gives mainly the tetrahydrocarbazole and glacial acetic acid mainly the tetrahydrocarbazolenine, thus substantiating the results already quoted. An *a priori* hypothesis would predict, by qualitative reasoning, that the stronger acid (sulphuric) should produce a greater proportion of base, whereas the reverse has been found to be the case. This marked difference could be ascribed to different mechanisms operating in these two reactions, although a number of other factors must be considered before any definite conclusion is reached.

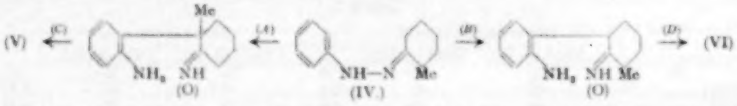
One noteworthy difference is that with glacial acetic acid only one phase is present and in

dilute sulphuric acid two phases are involved. This may be paralleled with the fact that the Cannizzaro reaction (cf. Alexander, *J. Amer. Chem. Soc.*, **1947**, **69**, 289) probably proceeds *via* a different mechanism dependent on whether or not the reaction is homogeneous. When the phenylhydrazone of 2-methylcyclohexanone (IV) was cyclised in aqueous acetic acid containing 20, 40, 60, 80, and 89% of water (by volume) respectively, the percentage yield of the major product, 11-methyltetrahydrocarbazolenine (V), was 56, 55, 57, 58, and 40% compared with 61% when glacial acetic acid was used. In the first case the reaction mixture was homogeneous throughout, in the second case it was initially heterogeneous and became homogeneous on heating, and in the last three cases it was heterogeneous throughout. It thus appeared that the reaction was not influenced by the number of phases present.

It was thus possible that the difference in reaction may be ascribed to the acid strength of the cyclising agent. When (IV) was refluxed with aqueous solutions of approximately equal molar strength of acetic, monochloro- dichloro- and trichloro-acetic acid, the yields of (V) were 40, 42, 51, and 53% respectively (*N.B.* all these reaction mixtures were heterogeneous). The *K* values of these acids are $1{\cdot}85 \times 10^{-5}$, $1{\cdot}55 \times 10^{-3}$, $5{\cdot}14 \times 10^{-2}$ and $1{\cdot}2 \times 10^{0}$ (?) and yet it is seen that the relative yields of (V) do not vary markedly and tend to increase with increasing acid strength. In view of the remarkable difference between the action of glacial acetic acid and dilute sulphuric acid, this result is very confusing, particularly when it is realised that trichloroacetic acid approaches sulphuric acid in strength, although it has been found that trichloroacetic acid is weaker than sulphuric acid in strong (>2N.) solutions. Thus it would appear that acid strength is not the deciding factor.

Finally, it was considered that as the apparently heterogeneous reaction in aqueous acetic acid gave the same results as when glacial acetic acid was used, the reaction may actually take place in a single phase, as the hydrazone will be partly soluble in the boiling aqueous acetic acid. On the other hand, it would be virtually insoluble in the aqueous sulphuric acid and so the difference between these two reactions may, after all, be due to the number of phases. Accordingly, the cyclisation of (IV) was investigated using alcoholic solutions of sulphuric acid and anhydrous hydrogen chloride. Under these conditions, the initial reactants were soluble, as were the products, with the exception of salts which precipitated during the reaction when hydrogen chloride was used. In the case of sulphuric acid, it was found that although the yield of (V) was greater and the yield of 1-methyltetrahydrocarbazole (VI) was correspondingly smaller, when alcohol was substituted for water as a diluent, the yield of (V) did not approach that obtained with glacial acetic acid. In the case of hydrogen chloride also, the alcoholic solution gave a larger yield of (V) than did the aqueous solution. It may be noted that hydrochloric acid gave a higher yield of (V) than aqueous sulphuric acid of approximately the same normality. Finally dry gaseous hydrogen chloride and a solution of (IV) in dry boiling benzene gave the most surprising results since the yield of (V) was then even greater than with glacial acetic acid and only a very little (VI) was obtained.

In order to harmonise these apparently conflicting findings, it is supposed, on the basis of the accepted mechanism for this reaction (for a summary, see Pausacker and Schubert, *loc. cit.*), that the reaction may proceed as follows:



Now the cyclising agents which favour the formation of (V) are glacial acetic acid, aqueous solutions of acetic acid and its three chloro-derivatives, and hydrogen chloride in benzene The other reagents, in the order in which they favour the yield of (VI), are aqueous sulphuric acid, aqueous hydrogen chloride, alcoholic sulphuric acid, and alcoholic hydrogen chloride. Mr. A. N. Hambly, of this Department, has kindly pointed out that of the first series of media, acetic acid and benzene are protogenic and aprotic respectively, whereas in the latter series both ethyl alcohol and water used are amphiprotic. This suggests that when we have a medium which permits the manifestation of the basic properties of (IV) (*i.e.*, reaction with a proton), then reaction *A*, followed by reaction *C*, is favoured. On the other hand, a medium which tends to decrease the basic characteristics of (IV), by competitive reaction with protons, favours reaction *B* which possibly proceeds by a different mechanism from reaction *A*. Thus the order observed for the second series of solvents may also be explained as water is more protophilic than alcohol and, in addition, there are some indications (cf. "Introduction to

Electrochemistry," Glasstone, p. 310) that sulphuric acid may be more protophilic than hydrochloric acid.

It would now seem that when aqueous solutions of the various acetic acids are used, the reactions must take place in a medium which favours the basic behaviour of (IV). This fact may be accommodated by assuming that the various acetic acids may be dissolved partly in the water and partly in the (IV) (in contrast to the statement made above) and the reaction leading to the principal formation of (V) actually takes place in the acetic acid–(IV) phase.

Thus the different actions of these cyclising agents may be explained by assuming that (IV) has a different proton affinity in the various media used. Up to now, the different formulations of the mechanism of the Fischer indole synthesis have not taken into account the exact role played by the acid catalyst. It would appear in the reaction studied that two alternative mechanisms are simultaneously possible, dependent on the relative proton availability present in the medium. Thus, in future discussions of this reaction it will be necessary to consider, in greater detail, the part played by the catalyst. A kinetic investigation of this reaction is now proceeding with this aim in view.

Experimental.

M. p.s are not corrected.

Preparation of 2-Substituted cyclo*Hexanones.*—2-Methyl-, 2-ethyl-, and 2-*iso*propyl-*cyclo*hexanone were prepared by alkaline hydrolysis of the corresponding 2-carbethoxy-2-alkyl-*cyclo*hexanones, produced by condensation of the appropriate alkyl iodide with the sodio-derivative of 2-carbethoxy-*cyclo*hexanone.

2-*cyclo*Hexyl*cyclo*hexanone was prepared by chromic acid oxidation of 2-*cyclo*hexyl*cyclo*hexanol (cf. Ungnade, *J. Org. Chem.*, 1948, **13**, 361).

2-Phenyl*cyclo*hexanone was prepared by the action of phenylmagnesium bromide on 2-chloro*cyclo*hexanone (Newman and Farbman, *J. Amer. Chem. Soc.*, 1944, **66**, 1551).

Preparation of the Phenylhydrazones.—Equimolar amounts of phenylhydrazine and *cyclo*hexanone were heated (0·5 hour) on the water-bath, first at atmospheric pressure and then under reduced pressure until all the water was expelled.

Cyclisations of the Hydrazones.—The hydrazones were refluxed (0·5 hour) with aqueous sulphuric acid (1 ml. of concentrated acid and 9 ml. of water per g. of hydrazone) or glacial acetic acid (9 ml. per g. of hydrazone). When sulphuric acid was used, the neutral fraction was isolated by extraction with ether and washing first with dilute sulphuric acid and then with water. The 1-substituted tetrahydrocarbazole was isolated by distillation. The sulphuric acid solution and washings were basified with sodium hydroxide solution, and the 11-substituted tetrahydrocarbazolenine isolated by ether-extraction, followed by distillation. When glacial acetic acid was used, the excess of acid was removed by distillation under reduced pressure and the residue treated with water, extracted with ether, and separated into neutral and basic fractions as described above. For yields see Table I. Tables II and III summarise the physical, chemical, and analytical data.

Table II.

1-*Substituted tetrahydrocarbazoles.*

	Base.					Picrate.		
Substituent.	B. p./mm.	Formula.	Found: N, %.	Reqd.: N, %.	M. p.[a]	Found: N, %.	Reqd.: N, %.
Ethyl[a]	184—186°/0·8	—	—	—	142°[b]	13·2	13·1
*iso*Propyl	190°/0·6	$C_{14}H_{19}N$	6·9	6·6	117[c]	13·1	12·7
*cyclo*Hexyl	195°/0·4	$C_{18}H_{23}N$	5·6	5·5	140[d]	12·1	11·6
Phenyl[b]	187°/0·3[e]	$C_{18}H_{17}N$	5·8	5·8	133[f]	11·9	11·7

[a] Lions (*loc. cit.*) gives b. p. 200—205°/16 mm. [b] Appreciable amounts of 2-phenyl*cyclo*hexanone were also obtained when dilute sulphuric acid was used. [c] M. p. 99°; crystallised from light petroleum (b. p. 40—60°). [d] Crystallisation from light petroleum of b. p.: [e] 100—120°, [f] 60—90°, [g] 95—135°.

Table III.

11-*Substituted tetrahydrocarbazolenines.*

	Base.						Picrate.		
Substituent.	B.p./mm.	M. p.[b]	Formula.	Found: N, %.	Reqd.: N, %.	M. p.	Solvent.[d]	Found: N, %.	Reqd.: N, %.
Ethyl[a]	142°/1·0	—	$C_{14}H_{17}N$	—	—	152°[c]	A	12·8	13·1
*iso*Propyl	166°/0·5	81°	$C_{15}H_{19}N$	6·3	6·6	178	B	13·1	12·7
*cyclo*Hexyl ...	164°/0·4	79	$C_{18}H_{23}N$	5·9	5·5	171	A	11·6	11·6
Phenyl	184°/1·0	125	$C_{18}H_{17}N$	5·6	5·8	184	A	11·9	11·7

[a] Lions (*loc. cit.*) gives b. p. 160—161°/16 mm. [b] Crystallised from light petroleum (b. p. 40—60°). [c] Lions (*loc. cit.*) gives m. p. 147°. [d] Solvents: A, ethanol; B, light petroleum (b. p. 100—120°).

Dehydrogenation of the Tetrahydrocarbazoles to form Carbazoles.—The 1-substituted carbazole (1·0 g.) was heated for 4 hours at 280—300° with palladised charcoal (0·25 g.) in a stream of hydrogen. The product was extracted with acetone and crystallised from light petroleum (b. p. 40—60°) after distilling off the acetone. The physical, chemical, and analytical data are summarised in Table IV. Picrates were crystallised from benzene.

TABLE IV.

1-Substituted carbazoles.

	Base.				Picrate.		
Substituent.	M. p.	Formula.	Found: N, %.	Reqd.: N, %.	M. p.	Found: N, %.	Reqd.: N, %.
Ethyl	74°	$C_{14}H_{13}N$	7·1	7·2	158°	13·15	13·2
iso-Propyl	64	$C_{15}H_{15}N$	7·1	6·7	152	12·8	12·8
Phenyl	133	$C_{18}H_{13}N$	5·7	5·8	151	12·4	11·9

Cyclisation of the Phenylhydrazone of 2-Methylcyclohexanone in Various Conditions.—The hydrazone (30 g.) was refluxed for 0·5 hour with the cyclising agents shown in Table V and then worked up as described above. When extraction indicated a small yield of 1-methyltetrahydrocarbazole (VI), only the 11-methyltetrahydrocarbazolenine (V) was purified by distillation.

TABLE V.

Cyclising agent, nature.	amount.	Water, ml.	% Yields of (V).	(VI).	Cyclising agent, nature.	amount.	Water, ml.	% Yields of (V).	(VI).
AcOH,	270 ml.	—	61	6	$CCl_3{\cdot}CO_2H$,	77·5 g.	191	53	—
,,	216 ml.	54	56	—	Conc. H_2SO_4,	30 ml.	270	21	45
,,	162 ml.	108	55	—	,,	30 ml.	(EtOH, 270 ml.)	36	33
,,	108 ml.	162	57	—					
,,	54 ml.	216	58	—	Conc. HCl,	108 ml.	192	38	40
,,	27 ml.	214	40	—	HCl, gas,	44 g.	(EtOH, 270 ml.)	44	19
$CH_2Cl{\cdot}CO_2H$,	45 g.	206	42	—					
$CHCl_2{\cdot}CO_2H$,	61 g.	201	51	—	C_6H_6 *	270 ml.	—	65	4

* Continuously saturated with dry HCl.

Analyses are by Messrs. N. Lottkowitz and N. Gamble. The author thanks his colleagues for many helpful discussions.

UNIVERSITY OF MELBOURNE. [*Received, September 9th*, 1949.]

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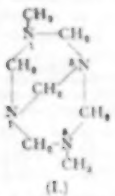
120. *On the Structure of Knudsen's Base and of Related Compounds. Part I.*

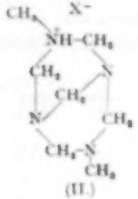
By M. E. FOSS, E. L. HIRST, J. K. N. JONES, H. D. SPRINGALL, A. T. THOMAS, and T. URBAŃSKI.

The corresponding salts of Knudsen's base, and those of the base obtained by treating hexamine dinitrate with hot solvents, are identical with one another and with the corresponding salts of the 1-methylhexamine ammonium cation.

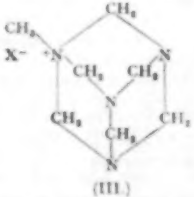
KNUDSEN (*Ber.*, 1914, **47**, 2694) described the preparation of a base, since called "Knudsen's base," in the form of its sulphate, by the action of aqueous formaldehyde on ammonium sulphate. On the basis of carbon, hydrogen, and nitrogen analyses of the salts, Knudsen assigned to the base the structure (I), 1 : 5-dimethylpentamethylenetetramine. The salts were regarded as hydrosalts of type (II).



(I.)



(II.)



(III.)

We had found that, when hexamine dinitrate is treated with hot water, methyl alcohol,

ethyl alcohol, *iso*propyl alcohol, or *tert.*-butyl alcohol, the main product isolated, the nitrate, m. p. 195°,* of an organic base (*A*), is independent of the solvent. This compound was identified by carbon, hydrogen, nitrogen, " CH_2 as CH_2O," and nitrate ion analyses, and by mixed m. p., as the hexamine methonitrate (1-methylhexamine 1-nitrate) (III; X = NO_3) prepared by Hahn and Walter (*Ber.*, 1921, **54**, 1531) by addition of methyl nitrate to hexamine. This compound was also prepared *via* hexamine methiodide and most carefully investigated in the University of Pennsylvania where it was independently shown that, when hexamine dinitrate is extracted with hot chloroform, hexamine methonitrate is produced (private communication from Professor Marvin Carmack).

We then noticed that corresponding salts of base *A* and of Knudsen's base had many identical chemical and physical properties, indicating that the two bases probably have identical structures. If this is so, then, either the identification of the salts of base *A* as (III), or Knudsen's formulation of the salts of his base as (II), must be in error, and in this connection we note the observation of Hahn and Walter (*loc. cit.*) who had prepared a compound by a reaction similar to Knudsen's reaction (using aqueous formaldehyde, ammonia, and ammonium sulphate) and designated it as (III; X = $NH_4SO_4^-$) on the basis of analyses for carbon, hydrogen, nitrogen, and sulphur only. They did not consider the alternative structure and do not refer to Knudsen's work.

It was therefore decided to re-examine the points named in the headings below.

Evidence for the Identification of the Salts of Base A *as having Structure* (III).—This problem is treated in two parts, showing (*a*) that the main product *A* is the same for a range of solvents, and (*b*) that the product *A* is a nitrate having structure (III; X = NO_3).

(*a*) The analytical data and the m. p. and mixed m. p. data for the products *A* isolated by treatment of hexamine dinitrate with several hot solvents are given in Table I and leave little doubt that the various products are identical.

(*b*) The identification of the product *A* as (III; X = NO_3) was carried out on the specimen obtained by hot water. The analytical results for the nitrate, picrate, and chloride are given in Table III. For all three, the theoretical figures for carbon, hydrogen, nitrogen, and anion are so similar for the alternative structures (II) and (III) that no differentiation on this basis can be made. The theoretical figures for *N*-methyl and methylene, however, are markedly different, and the experimental data favour the formulation (III) (methylhexamine salts).

TABLE I.

Substance *A* prepared by	C, %.	H, %.	N, %.	CH_2, %.	NO_3^-, %.*	M. p.	Mixed m. p.
H_2O	38·8	6·9	32·2	38·4	28·2	192°	190°
MeOH	38·5	7·0	33·0	38·2	28·0	190	
EtOH	38·9	6·8	32·4	38·6	28·3	191	191
Pr^iOH	38·8	6·9	32·5	38·0	28·2	192	190
Bu^nOH	38·7	6·9	31·9	38·1	28·3	192	190
$CHCl_3$ *	39·0	7·0	32·6	—	27·4	193	

The analytical data reported in this paper were obtained as follows: The C, H, N, and *N*-CH_3 (Herzig–Meyer) determinations were by Drs. Weiler and Strauss (Oxford); CH_2 was determined gravimetrically as CH_2O by dinitrophenylhydrazine, following Brady (*J.*, 1931, 757); NO_3^- and picrate$^-$ were determined by nitron, following Cope and Barab (*J. Amer. Chem. Soc.*, 1917, **39**, 509); Cl^- was determined as AgCl.

* Data obtained in the University of Pennsylvania (private communication from Professor Marvin Carmack).

TABLE II.

Base.	M. p. of salt. Nitrate.	Picrate.	Chloride.
(*a*) Authentic methylhexamine	190°	210°	—
(*b*) Base *A* (hot H_2O)	192	212	202°
(*c*) Knudsen's base	190	209 *	202
Mixed *a*–*b*	190	212	—
Mixed *b*–*c*	190	209 *	202

* Data obtained by A. T. T. and T. U. at Explosives Research and Development Establishment (E.R.D.E.). The m. p. of this picrate is discussed below.

As was expected, *N*-methyl determinations were not very satisfactory. The Herzig–Meyer micro-procedure might well lead to anomalous results with compounds capable of yielding

* The melting of this substance, and of all other new substances discussed in this work, is accompanied by decomposition.

relatively large amounts of formaldehyde, especially with a tetra-alkylammonium cation such as in (III).

TABLE III.

Analysis of salts of base A *and Knudsen's base.*

	C, %.	H, %.	N, %.	*N*-CH_3, %.	CH_3, %.	Anion, %.	
Found for base *A*	38·8	6·9	32·2	10·0	38·4	28·2	nitrate
Found for Knudsen's base	38·7	7·4	32·2	9·8	38·5	28·3	
Calc. for $C_7H_{15}O_3N_5$ (III; X = NO_3)	38·7	6·9	32·3	13·4	38·8	28·6	
Calc. for $C_7H_{11}O_9N_5$ (II; X = NO_3)	38·4	7·8	32·0	26·5	32·0	28·3	
Found for base *A*	40·6	4·7	25·4	5·0	21·8	59·7	picrate
Found for Knudsen's base	40·6	4·6	25·6	5·2	21·5	59·3	
Calc. for $C_{13}H_{17}O_7N_7$ (III; X = picrate)	40·8	4·4	25·6	7·6	22·0	59·6	
Calc. for $C_{13}H_{13}O_7N_7$ (II; X = picrate)	40·6	5·0	25·5	15·1	18·2	59·3	
Found for base *A*	43·5	8·9	29·8	12·6	43·8	18·7	chloride
Found for Knudsen's base	43·7	9·0	29·5	11·9	44·0	18·7	
Calc. for $C_7H_{15}N_4Cl$ (III; X = Cl)	44·1	7·9	19·4	15·2	44·1	18·6	
Calc. for $C_7H_{11}N_4Cl$ (II; X = Cl)	43·6	8·8	29·1	30·1	36·4	18·4	

Authentic specimens of hexamine methonitrate and methopicrate (III; X = NO_3 or picrate) were prepared from hexamine by the successive action of methyl iodide and silver nitrate or picric acid. Mixed m. p.s of each of these substances and of the corresponding salts of base *A* are given in Table II.

The identity of authentic hexamine methonitrate and the nitrate of base *A* obtained by chloroform has been established by Dr. A. T. Blomquist of Cornell University by microscopic examination (private communication from Professor Marvin Carmack).

As a final check, specimens of authentic hexamine methopicrate and the picrate of base *A* (obtained by hot water) were submitted to Professor F. J. Llewellyn (then of Birmingham University) for comparison by the *X*-ray powder method. He reported that the specimens gave identical patterns (Fig. 1).

The identity of the salts of base *A* with the corresponding salts of the methylhexamine cation is thus established.

Comparison of the Properties of Corresponding Salts of Base A *and of Knudsen's Base.*—Hot water was used to produce the base *A*. The nitrates, picrates, and chlorides of base *A* and of Knudsen's base were prepared and analysed (see Tables II and III). The oily hydroxides prepared from the two bases had identical refractive indices (1·4475 at 20°).

It was found that aqueous solutions of the nitrate, chloride, dichromate, neutral sulphate, and hydroxide of base *A*, on treatment with aqueous picric acid, all gave the same picrate, m. p. 208—209° (m. p.s determined at E.R.D.E.), seemingly identical with the picrate obtained from Knudsen's base.

The findings presented in this section seem to indicate strongly the probable identity of the two bases.

Evidence for the Formulation of the Salts of Knudsen's Base.—The two lines of work described above indicate that salts of Knudsen's base have structure (III), whereas Knudsen (*loc. cit.*) had advocated structure (II). Its picrate was therefore subjected to tests analogous to those used for the identification of the picrate of base *A*.

The first batches of the picrate of Knudsen's base prepared in Manchester (M. E. F., E. L. H., J.-K. N. J., H. D. S.) had the m. p. 210° reported from E.R.D.E. All subsequent preparations gave the m. p. 195° recorded by Knudsen. The two specimens of hexamine methopicrate first prepared gave the expected m. p. 210—212°, but a mixed m. p. between them and Knudsen's picrate, m. p. 195°, gave no depression below 195° and all subsequent preparations of hexamine methopicrate in Manchester have shown m. p. 195—198°. It seems probable that hexamine methopicrate is dimorphic and that, the lower-melting dimorph being now obtained, we shall not be able to make again the other modification.

X-Ray powder photographs of Knudsen's picrate and of authentic hexamine methopicrate, kindly supplied by Professor F. J. Llewellyn, showed complete identity (Fig. 2), thus confirming the analytical data—the CH_3 content figure being especially significant—and the rather slight m. p. data.

Further evidence for the methylhexamine cation structure for Knudsen's compounds is furnished by our observation that the direct synthesis of the parent hydroxide of these compounds can be achieved from formaldehyde, methylamine, and ammonia, and that the yield

FIG. 1.

X-Ray powder diagrams for hexamine methopicrate (north and south quadrants) and the picrate of base A *(east and west quadrants).*

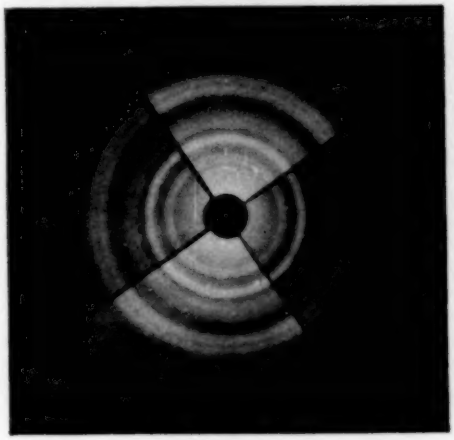
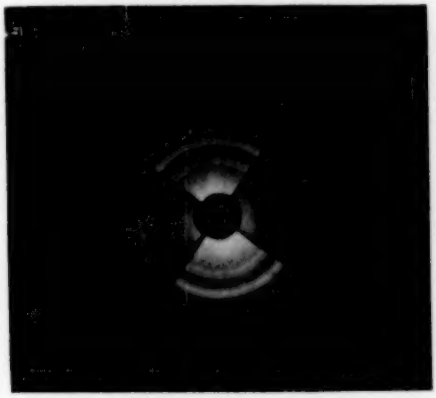


FIG. 2.

X-Ray powder diagrams for hexamine methopicrate (north and south quadrants) and the picrate of Knudsen's base (east and west quadrants).



[*To face p.* 456.

is much better (70%) when the reagents are mixed in the correct stoicheiometric proportions for structure (II; X = OH) (yield 50%).

Experimental.

(Analytical data quoted in the tables are not repeated below.)

Hexamine Dinitrate–Solvent Reactions. Base A.—(a) Water. Hexamine dinitrate (100 g.) and water (500 ml.) were refluxed for 1½ hours. The resulting solution was cooled, neutralised with aqueous sodium carbonate, and evaporated to dryness. The residue was extracted with hot methyl alcohol, and the extract cooled. The white needles deposited were recrystallised from alcohol. The nitrate of base *A* had m. p. 192° (6·5 g.).

The methyl-alcoholic filtrate was evaporated yielding a syrup (52 g.), which was dissolved in cold nitric acid (150 ml. of 70%). Methyl alcohol was added carefully, producing a white crystalline precipitate, which was collected, washed with cold ether, and dried in air. This compound, m. p. 140—145° (11 g.), differs from the above nitrate in being insoluble in hot dioxan, acetone, or acetic acid. It gives a strongly acidic solution in water which with the calculated amount of *N*/10-sodium hydroxide gives the nitrate, m. p. 192—195°, in good yield. The compound, m. p. 142°, is probably 1-methylhexamine 1 : 5-dinitrate (Found : C, 30·1; H, 5·6; N, 20·5; CH_2, 31·1; NO_3^-, 44·5. Calc. for $C_7H_{16}O_6$: C, 30·0; H, 5·7; N, 30·0; CH_2, 30·0; NO_3^-, 44·3%).

The nitrate of base *A* was prepared in better yield as follows. Hexamine dinitrate (25 g.) in water (50 ml.) was refluxed for 2½ hours, and then cooled and evaporated under reduced pressure. The crystalline residue, recrystallised from alcohol, had m. p. 190° (9 g.).

(b) Methyl alcohol. Hexamine dinitrate (40 g.) was refluxed in methyl alcohol (200 ml.) for 4 hours, evaporated under reduced pressure to 50 ml., and then kept at 0° overnight. The crystals which separated were recrystallised twice from alcohol, giving a nitrate as white needles, m. p. 190° (3·2 g.).

Similar experiments with the dinitrate (40 g.) and ethyl, *iso*propyl, and *tert.*-butyl alcohol gave the nitrate in yields of 3·5 g. (see Table I).

Salts of Base A (*obtained by hot* H_2O).—*Picrate.* To the nitrate (10 g.) in water (150 ml.), saturated aqueous picric acid was added at 0° until no further precipitation occurred. The orange-red picrate, recrystallised from hot water, had m. p. 208° (12 g.).

Chloride. Prepared as was the corresponding nitrate, starting from hexamine hydrochloride, this was obtained as white needles, m. p. 202° (after softening at 130°, and hardening at 135°) (yield 10—15%). It was also isolated, in good yield, from the filtrate from the precipitation of the nitrate of base *A* by nitron hydrochloride (Found : C, 43·5; H, 8·9; N, 29·8; Cl^-, 18·3. Calc. for $C_7H_{15}N_4Cl$: C, 43·9; H, 7·9; N, 29·4; Cl^-, 18·7%).

Dichromate. Hexamine tetrachromate was prepared by the method of Cambier and Brochet (*Bull. Soc. chim.*, 1895, **13**, 400) by the action of aqueous chromium trioxide on aqueous hexamine. The tetrachromate (42 g.) and water (500 ml.) were heated for 1½ hours on the steam-bath (after the initial dissolution, a dark brown amorphous solid was precipitated). The suspension was cooled and filtered, and the filtrate evaporated to 200 ml. On cooling, orange-yellow crystals separated; when dried, these had m. p. 215° (7 g.) (Found : C, 32·0; H, 6·5; N, 21·1; Cr, 20·0. Calc. for $C_{14}H_{32}O_{14}N_4Cr$: C, 32·0; H, 5·7; N, 21·4; Cr, 20·6%).

Hydroxide. To the chloride (25 g.) in water (150 ml.), moist silver oxide, freshly prepared from silver nitrate (25 g.), was added and the resulting suspension was shaken vigorously for 6 hours at room temperature and then filtered. The filtrate was evaporated under reduced pressure. The oily residue (12 g.), n^{20} 1·4475, of the crude hydroxide was not further purified. The oil is hygroscopic and yields an alkaline solution from which the corresponding picrate can be precipitated in 80% yield.

Salts of Knudsen's Base.—Nitrate. This was prepared by a method analogous to that used by Knudsen for the sulphate : a solution of ammonium nitrate (150 g.) in a mixture of aqueous formaldehyde (215 g. of 40%) and water (150 ml.) was heated to 70—80° on a water-bath for 1 hour. The product, isolated as in the case of the nitrate of base *A* and recrystallised from alcohol, had m. p. 190° (12 g.).

Chloride. This was prepared (*a*) by Knudsen's alternative method from pre-formed hexamine, and (*b*) from the nitrate. (*a*) Hexamine (93 g.) was added to a solution of methylamine hydrochloride (90 g.) in hydrochloric acid (229 g.; *d* 1·16) at 20°. The mixture was warmed on a water-bath for ½ hour, and then cooled, neutralised with anhydrous sodium carbonate, and evaporated to dryness. Sodium and ammonium chlorides were removed by extracting the product with hot alcohol (750 ml.). On cooling, the alcoholic extract gave a crop of crystals, mainly methylamine hydrochloride (25 g.) which was collected. Evaporation of the filtrate to 250 ml. gave a mixture (39 g.) of methylamine hydrochloride and Knudsen's chloride. Fractional crystallisation from alcohol gave the chloride, m. p. 202° (8 g.). (*b*) The filtrate from the precipitation of the nitrate from Knudsen's nitrate by nitron hydrochloride was worked up by the usual procedure to give Knudsen's chloride in good yield.

Picrate. This was prepared in 80% yield by addition of picric acid solution to a solution of any of the other salts of Knudsen's base, or the hydroxide.

Hydroxide. This was prepared from the chloride by the method used for base *A*.

Derivatives of 1-*Methylhexamine* (*Hexamine Metho-salts*).—*1-Nitrate.* Hexamine methiodide was prepared by refluxing, for 1 hour, hexamine (35 g.) suspended in methyl alcohol (250 ml.) and methyl iodide (40 g.). The methiodide was treated directly in hot methyl-alcoholic solution with powdered silver nitrate (43 g.). The whole was refluxed for ½ hour, and the resulting suspension was cooled and filtered. The methyl-alcoholic filtrate was worked up as for the nitrate of base *A* prepared by methyl alcohol. The product crystallised in colourless needles, m. p. 190° (40 g.).

1-Picrate. This was prepared by adding an equimolecular proportion of picric acid in saturated alcoholic solution at 60° to a solution of authentic hexamine methonitrate in alcohol at 60°. The resulting system was cooled to 0°; the product, hexamine methopicrate, when dried, formed orange-yellow needles, m. p. 210° (85%).

1-*Hydroxide*. This was synthesised from formaldehyde, ammonia, and methylamine as follows. (*a*) Using stoicheiometric proportions of the reagents correct for (III; X = OH). Paraformaldehyde (18 g., 0·6 mol.) was added to a solution of ammonia (17·5 ml., 0·3 mol.; *d* 0·880) and methylamine (9·5 ml., 0·1 mol.; 33%) at room temperature; the paraformaldehyde slowly dissolved, dissolution being accompanied by slight evolution of heat. The solution was kept overnight and then evaporated at 50°/20 mm. The product was extracted with ether, the ethereal solution dried and evaporated, and the product was finally dried *in vacuo* (12 g., 70%). (*b*) Using the stoicheiometric proportions of reagents correct for (II; X = OH), *i.e.*, paraformaldehyde (18 g., 0·6 mol.), ammonia (11 ml., 0·6 mol.; *d* 0·880), and methylamine (19·0 ml., 0·2 mol.; 33%). The yield was 9·5 g. (50%).

The authors acknowledge the assistance of Professor F. J. Llewellyn with the *X*-ray powder photography, helpful discussions with Dr. E. Roberts (E. R. D. E.), Dr. A. Carruthers and Dr. N. H. Woodbury (Bristol), and Dr. F. B. Strauss (Oxford), and extensive private communications from Professor Marvin Carmack (University of Pennsylvania). The authors thank the Chief Scientist of the Ministry of Supply for permission to publish this paper.

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EXPLOSIVES RESEARCH AND DEVELOPMENT ESTABLISHMENT,
MINISTRY OF SUPPLY.

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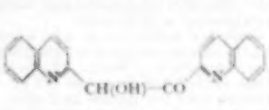
121. *Cyclic Meso-ionic Compounds derived from Quinoline.*

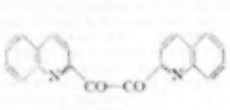
By B. R. BROWN and D. LL. HAMMICK.

A new class of compound, produced by the action of cyanide or cyanide-type ions on aldehydes of the quinoline and *iso*quinoline series, is described. The evidence for regarding them as possessing meso-ionic structures (IV) is reviewed. We propose to call them quinocolls, a systematic name for them being 3 : 6-dihydroxydiquinolino(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)-pyrazinium dihydroxide bisanhydro-salts. A mechanism for their production is suggested.

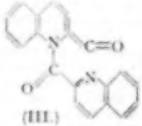
HENZE (*Ber.*, 1934, **67**, 753) reports that quinaldoin (I), m. p. 261°, is produced by the action of aqueous-alcoholic potassium cyanide on quinoline-2-aldehyde. No analysis or chemical properties of the compound are given. Kaplan (*J. Amer. Chem. Soc.*, 1941, **63**, 2654) confirmed this work and recorded an analysis. He also obtained the compound (very pale brown needles, m. p. 269—271°) by the action of old selenium dioxide on quinaldine in dioxan. By analogy with the formation of benzoin from benzaldehyde and potassium cyanide, Kaplan assumed that the compound was quinaldoin (I), but recorded no chemical properties. Later Linsker and Evans (*ibid.*, 1946, **68**, 947) obtained a compound, m. p. 175°, which they formulated as quinaldil (II), from the reaction of selenium dioxide with quinaldine. This reacted with urea in the same way as does benzil, and on reduction yielded a compound, m. p. 135°, which had the chemical properties expected for quinaldoin (I).



(I.)



(II.)



(III.)

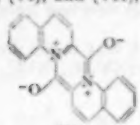
By the decarboxylating action of picolinic or quinaldinic acid on quinoline-2-aldehyde we have obtained a compound in the form of colourless needles, m. p. 266—267°, which proved to be identical with the compound produced from quinoline-2-aldehyde and potassium cyanide. This is a further example of the analogous chemical behaviour of the cyanide ion and the ions resulting from the decarboxylation of picolinic and quinaldinic acids (Dyson and Hammick, *J.*, 1937, 1724; Ashworth, Daffern, and Hammick, *J.*, 1939, 809; Brown and Hammick, *J.*, 1949, 173).

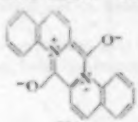
The compound dissolves in concentrated hydrochloric acid and in 30% sulphuric acid to a yellow solution. It forms a yellow *diperchlorate*. Oxidation with potassium permanganate in hot aqueous pyridine yields 77% of quinaldinic acid. The compound reacts vigorously with hot concentrated aqueous potassium hydroxide to yield 60% of potassium quinaldinate. This reaction proceeds with simultaneous reduction of added methylene-blue. Boiling aniline converts the compound into the anilide of quinaldinic acid. The compound is inert towards carbonyl or hydroxyl group reagents under a variety of conditions, and is unaffected by cold potassium permanganate solution or by bromine water.

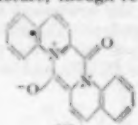
Elementary analysis of the compound agrees better with the empirical formula $C_{20}H_{12}O_2N_2$ than with $C_{20}H_{14}O_2N_2$ [cf. Kaplan (*loc. cit.*) whose analysis also agrees better with $C_{20}H_{12}O_2N_2$].

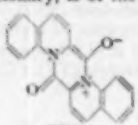
A molecular-weight determination proved impossible owing to insolubility of the compound in suitable solvents. However, a dimethyl analogue produced from ***3-methylquinoline-2-aldehyde*** and potassium cyanide is more soluble, and a molecular-weight determination in camphor indicates that its molecular formula is $C_{22}H_{14}O_2N_2$, *i.e.*, that it corresponds with a molecular formula of $C_{20}H_{12}O_2N_2$ for the original compound. Thus in its formation from two molecules of quinoline-2-aldehyde two hydrogen atoms must be lost: $2C_{10}H_7ON = C_{20}H_{12}O_2N_2 + 2H$. This was established by the observations that added methylene-blue is reduced and the compound produced when an aqueous-alcoholic solution of quinoline-2-aldehyde is treated with aqueous potassium cyanide.

The experiments of Linsker and Evans (*loc. cit.*) together with the chemical evidence which we have obtained (lack of carbonyl or hydroxyl group reactivity) indicate that the compound is neither quinaldoin (I) nor quinaldil (II). Furthermore, Mr. B. H. Thewlis working in this laboratory has independently synthesised quinaldil (II), which is identical with the compound of Linsker and Evans, from 1 : 2-di-2′-quinolylethane. Another possibility, the keten structure (III), is eliminated on account of the stability of the compound towards reagents such as alcohol. The oxidation of the substance to quinaldinic acid necessitates the conclusion that only the α-carbon atoms and possibly the nitrogen atoms are involved in the fusion of the two quinoline nuclei which the molecular weight indicates. The physical properties of the substance (insolubility in common solvents and high m. p.) indicate that it has a salt-like structure. This, together with the fact that the obvious structures have been eliminated, leads us to suggest that the compound has the structure of a zwitterion. A few of the contributing canonical forms, (IV), (V), (VI), and (VII), are shown below. This structure, though revoluntionary, is of the type

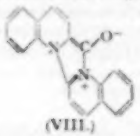

(IV.)

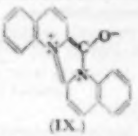

(V.)

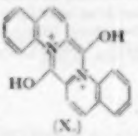

(VI.)

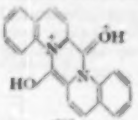

(VII.)

called " meso-ionic " by Baker, Ollis, and Poole (*J.*, 1949, 307), and is analogous to the formulæ which they have proposed for the sydnones. A much closer parallel is the zwitterion formula (VIII)—(IX), suggested by Krollpfeiffer and Schneider (*Annalen*, 1937, **530**, 34) for Besthorn's red, a compound produced by the decarboxylation of quinaldinic acid in acetic anhydride (Besthorn and Ibele, *Ber.*, 1904, **37**, 1236; 1905, **38**, 2127). Since in the resonance hybrid of the new structure, comprising (IV), (V), (VI), and (VII), there is no actual shift of electronic charge


(VIII.)

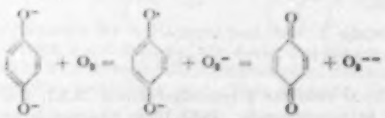

(IX.)


(X.)

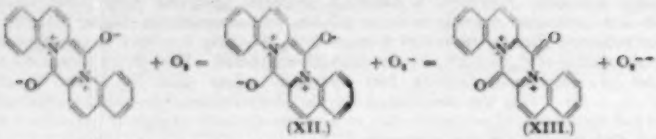

(XI.)

the compound is expected to be colourless. Besthorn's red provides an interesting contrast, since in the molecule of this compound the positive charge is asymmetrically distributed across a conjugated system. On reaction with a strong acid (*e.g.*, sulphuric or perchloric) the compound (IV) can act as a diacidic base yielding a cation capable of formulation in terms of canonical forms such as (X) and (XI). Consequently, on account of the asymmetry and mobility of the positive charge, it is not surprising that this cation is yellow.

The autoxidation and alkaline hydrolysis of the compound are particularly suggestive of the meso-ionic formula advanced. The structure suggested for the compound is similar to that of a quinol ion, and it is well known (Weissberger, Thomas, and Valle, *J. Amer. Chem. Soc.*, 1943, **65**, 1489) that in alkaline solution quinols readily undergo autoxidation to yield the corresponding quinones :


(Semiquinone)

A similar autoxidation of our compound would proceed as follows :

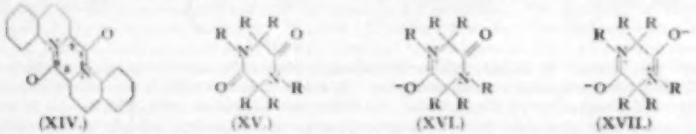


(XII.) (XIII.)

The product (XIII) is the cation of an acylquinolinium hydroxide, and hence would be expected to hydrolyse readily to quinaldinic acid. The formation of a semiquinone type of ion (XII) as an intermediate is suggested by the deep colour which appears and then fades as the reaction with alkali proceeds. The reaction with aniline producing the anilide of quinaldinic acid possibly involves a similar oxidative attack.

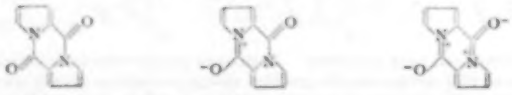
We have given the trivial name quinocoll to the structure, by analogy with the compound pyrocoll (XVIII) (Weidel and Ciamician, *Monatsh.*, 1880, **1**, 279; Ciamician and Silber, *Ber.*, 1884, **17**, 106) which has almost the same central ring fused to two pyrrole nuclei. The quinoline rings are numbered in the normal manner, so that the compounds (XXIII) and (XXIV) are respectively **3** : 3′-dimethyl- and **6** : 6′-dimethylquinocoll. We feel that for convenience it is desirable to have such a name, though it is also clearly necessary to have a systematic description. The Editor has suggested that the parent compound (IV) be called **3** : 6-dihydroxydiquinolino-(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)pyrazinium dihydroxide bisanhydro-salt, and that the numbering be as indicated (XIV). Thus the compound is regarded as the internal salt resulting from the dehydration of a phenolic ammonium hydroxide.

It is of interest to compare the central ring in this new structure with that in the diketopiperazines (XV), (XVI), and (XVII), and in the compound called pyrocoll (XVIII), (XIX), and



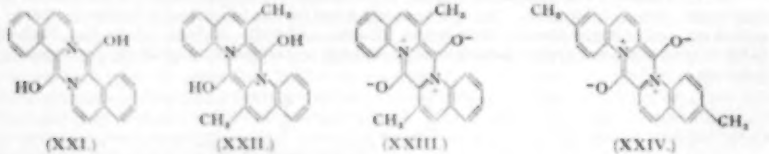
(XIV.) (XV.) (XVI.) (XVII.)

(XX) (*idem*, *ibid.*). The difference is to be found in the fact that the new structure is completely aromatic, the central ring containing six non-localised electrons. In the diketopiperazines and in pyrocoll the central ring contains only four non-localised electrons. This difference is reflected in the alkaline hydrolysis of these compounds, pyrocoll yielding pyrrole-2-carboxylic acid directly, but quinocoll undergoing simultaneous autoxidation and hydrolysis to yield quinoline-2-carboxylic acid.



(XVIII.) (XIX.) (XX.)

The reaction of quinoline-2- and *iso*quinoline-1-aldehydes with potassium cyanide to yield quinocolls appears to be quite general. Under these conditions *iso*quinoline-1-aldehyde and



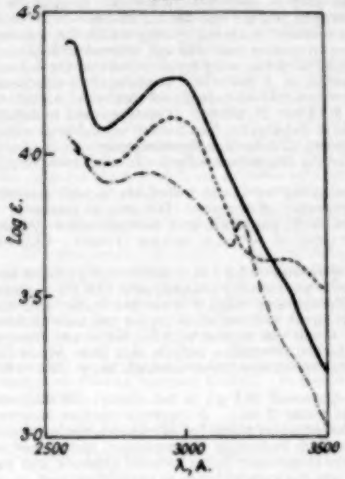
(XXI.) (XXII.) (XXIII.) (XXIV.)

3-methylquinoline-2-aldehyde yield the *dihydro*-derivatives (XXI) and (XXII), which exhibit none of the reactions of keto-compounds. Both these compounds are thermochromic, being

colourless in cold alcoholic solution and passing reversibly on being heated through yellow and orange to deep red. Both readily reduce methylene-blue, and (XXII) is oxidised by air to **3 : 3′-*dimethylquinocoll*** (XXIII). This compound does not readily undergo autoxidation and hydrolysis with alkali, possibly owing to a steric effect of the methyl groups adjacent to the central ring. **6-*Methylquinoline-2-aldehyde*** reacts with potassium cyanide to yield **6 : 6′-*dimethylquinocoll*** (XXIV) directly.

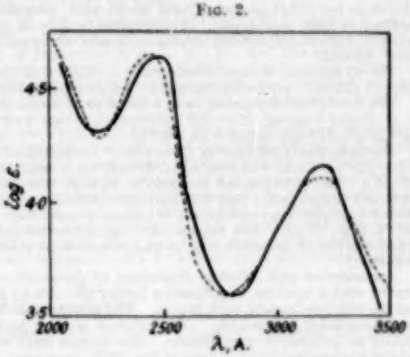
The isolation of dihydro-compounds which are readily oxidised to quinocolls indicates that the formation of the meso-ionic structure occurs by dimerisation of the quinoline-2-aldehyde under the influence of cyanide-type ions, followed by atmospheric oxidation of the resulting

Fig. 1.



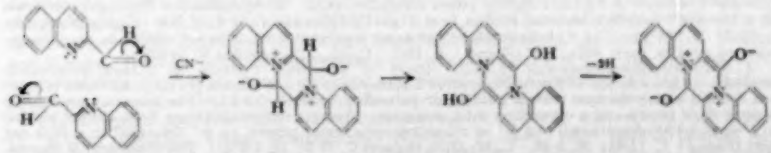
——— *Absorption spectrum of quinocoll in dioxan.*
– – – – *Absorption spectrum of* **3 : 3′-*dimethyl-quinocoll in dioxan.***
— · — · *Absorption spectrum of* **3 : 3′-*dimethyl-dihydroquinocoll in dioxan.***

Fig. 2.



——— *Absorption spectrum of quinocoll in 30% sulphuric acid.*
– – – – *Absorption spectrum of* **3 : 3′-*dimethyl-quinocoll in 30% sulphuric acid.***

dihydro-derivative. The processes involved are illustrated in a simple manner by the following tentative mechanism. An analogy for the initial addition is provided by the reaction between quinoline and benzaldehyde in sunlight, which yields 1-benzoyl-1 : 2-dihydroquinoline (Benrath, *J. pr. Chem.*, 1906, **73**, 384).



The ultra-violet absorption spectra of quinocoll and its **3 : 3′**-dimethyl analogue in dioxan and in 30% sulphuric acid (Figs. 1 and 2) leave little doubt that the compounds have analogous structures. The spectrum of **3 : 3′-dimethyldihydroquinocoll** in dioxan (Fig. 1) is very similar to those of ordinary quinoline derivatives, and differs markedly from the spectra of the quinocolls.

EXPERIMENTAL.

(M. p.s are uncorrected. Analyses are by Mr. F. C. Hall. Absorption spectra are by Dr. F. B. Strauss of Oxford.)

αα-Dibromoquinaldine •.—*αααα*-Tribromoquinaldine (48·0 g.) was heated in tetralin (80 ml.) at 100° for 12 hours. The resulting brown crystalline mass was diluted with light petroleum, and the light-brown crystals (34·4 g.) were recrystallised from alcohol. *αα*-Dibromoquinaldine was obtained as colourless needles, m. p. 119—120°. Hammick (*J.*, 1926, 1302) records m. p. 120°.

Quinocoll [3 : 6-*Dihydroxydiquinolino*(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)*pyrazinium Dihydroxide Bisanhydrosalt*] (IV).—(a) *By the action of potassium cyanide on quinoline-2-aldehyde* (Henze, *loc. cit.*; Kaplan, *loc. cit.*). The compound separated from pyridine as pale yellow needles, m. p. 266—267°. After treatment of a hot pyridine solution with a drop of acetic anhydride the compound crystallised as colourless needles, m. p. 266—267°. Henze (*loc. cit.*) gives m. p. 261°; Kaplan (*loc. cit.*) gives m. p. 269—271°.

(b) *By the decarboxylation of picolinic or quinaldinic acid in quinoline-2-aldehyde.* A mixture of picolinic or quinaldinic acid (0·2 g.) and quinoline-2-aldehyde (1·0 g.) was heated at 150—165° for 10 minutes. Carbon dioxide was evolved and a vigorous reaction occurred, during which the mixture darkened and completely solidified. The mass of dark brown needles was collected, washed with alcohol, and recrystallised several times from pyridine (plus a drop of acetic anhydride to remove the colour). The compound (0·7 g.) was thus obtained as colourless needles, m. p. 266—267°, unchanged on admixture with the compound obtained from the action of potassium cyanide on quinoline-2-aldehyde (Found: C, 76·9; H, 4·0; N, 9·2. Calc. for $C_{20}H_{12}O_2N_2$: C, 76·9; H, 3·85; N, 9·0%). The compound is slightly soluble in hot ethyl alcohol, glacial acetic acid, benzene, or chloroform, but almost insoluble in water, acetone, or light petroleum. It crystallises well from dioxan or from 2-methoxyethanol. It is soluble in concentrated hydrochloric or sulphuric acid with production of a yellow colour. It is insoluble in cold dilute alkalis.

The compound is unaffected under a variety of conditions by acetic anhydride, acetyl chloride, benzoyl chloride, phenylhydrazine, 2 : 4-dinitrophenylhydrazine, or bromine. It forms no picrate.

The *perchlorate* separated from a mixture of acetic and 60% perchloric acid as small yellow prisms, m. p. (rapid heating) 222—223° (decomp.), which were dried at 80° in a vacuum (Found: Cl, 14·4. $C_{20}H_{12}O_2N_2,2HClO_4$ requires Cl, 13·8%).

Permanganate Oxidation of Quinocoll.—A solution of quinocoll (0·5 g.) in a mixture of pyridine and water (20 ml. each) was treated at 90° during 2 hours with potassium permanganate (2·0 g.) in water (10 ml.). The precipitated manganese dioxide was collected and washed with hot water, and the colourless filtrate made just acid and again filtered. Treatment with excess of copper sulphate solution yielded a greyish-blue precipitate of copper quinaldinate, which was washed with hot water and dried at 100° (0·5 g., 77%). The copper salt was converted into the crystalline sodium salt from which the hydrochloride of quinaldinic acid was obtained as colourless needles (from alcohol), m. p. 192—196° (decomp.).

Autoxidation and Alkaline Hydrolysis of Quinocoll.—Quinocoll (0·5 g.) in hot dioxan (20 ml.) was treated with a solution of potassium hydroxide (2·0 g.) in water (3 ml.). A vigorous reaction occurred and the solution became dark brown. The mixture was boiled under reflux for 30 minutes, during which the colour faded appreciably. The aqueous layer of potassium hydroxide was separated and proved to contain no potassium quinaldinate. The dioxan layer was evaporated under reduced pressure, and the resulting potassium quinaldinate (0·4 g., 60%) converted into the hydrochloride of quinaldinic acid, m. p. 189—194° (decomp.).

Action of Aniline on Quinocoll.—Quinocoll (0·5 g.) was heated under reflux with redistilled aniline (15 ml.) for 4 hours. Initially the solution became very dark brown, but finally it had a clear yellowish-brown colour. Distillation with steam removed aniline, and on cooling the residual brown oil solidified. Two crystallisations from alcohol yielded colourless silky needles (0·4 g., 50%), m. p. 138—139° (Found: C, 77·7; H, 4·8; N, 11·0. Calc. for $C_{16}H_{11}ON_2$: C, 77·4; H, 4·8; N, 11·3%). On admixture with an authentic specimen of the anilide of quinaldinic acid (Krollpfeiffer and Schneider, *loc. cit.*) the m. p. was unchanged.

3-Methylquinoline-2-aldehyde.—*β*-(3-Methyl-2-quinolyl)acrylic acid (16·0 g.) (Brown, Hammick, and Robinson, *J.*, in the press), sodium carbonate solution (150 ml. of 6%), and benzene (100 ml.) were cooled in ice, stirred vigorously, and treated during 1 hour with powdered potassium permanganate (25·3 g.). The mixture was filtered, the manganese dioxide washed with ether, and the ether–benzene layer separated from the filtrate, washed with water, and dried. Removal of the solvents yielded *3-methylquinoline-2-aldehyde* (6·8 g.) as a slightly yellow crystalline solid. Recrystallisation from light petroleum (b. p. 80—100°) gave flat colourless needles, m. p. 114—115° (Found: C, 77·1; H, 5·3. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%). The 2 : 4-*dinitrophenylhydrazone* separated from xylene–pyridine as fine orange-coloured needles, m. p. 261—262° (Found: N, 19·7. $C_{17}H_{13}O_4N_5$ requires N, 19·9%).

3 : 3′-Dimethyldihydroquinocoll (XXII). *Action of Potassium Cyanide on 3-Methylquinoline-2-aldehyde.*—A hot solution of 3-methylquinoline-2-aldehyde (1·5 g.) in alcohol (15 ml.) and water (15 ml.) was treated under nitrogen with a solution of potassium cyanide (0·2 g.). The solution immediately became dark brown and a crystalline solid separated. Several recrystallisations from alcohol yielded *3 : 3′-dimethyldihydroquinocoll* (0·9 g.) as colourless rectangular prisms, m. p. 154—155° to a dark red melt (Found: C, 77·65; H, 5·45. $C_{22}H_{16}O_2N_2$ requires C, 77·2; H, 5·3%). The compound is thermochromic. Its cold alcoholic solution is colourless, but on being heated it passes slowly through yellow and orange to deep red. These colour changes are reversed as the solution cools. The compound is soluble in acids but not in alkalis. In air it slowly becomes light brown and falls to a powder. A hot alcoholic solution of the dihydro-compound quickly reduces and decolorises methylene-blue. It does not react with phenylhydrazine.

• The free-radical mechanism of this reaction will be discussed in a later publication.

3 : 3'-*Dimethylquinocoll* **[3 : 6-*Dihydroxy*-3' : 3''-*dimethyldiquinoline*(1' : 2' - 1 : 2)(1'' : 2'' - 4 : 5)-*pyrazinium Dihydroxide Bisanhydro-salt*]** (XXIII).—When **3 : 3'**-dimethyldihydroquinocoll is kept in air for several days the colourless rectangular prisms gradually change into a light-brown powder, which is only very slightly soluble in boiling alcohol. Recrystallisation from alcohol–pyridine yields **3 : 3'-*dimethylquinocoll*** as slightly brown needles, m. p. 220—221° (Found : C, 77·4; H, 4·8%; *M* (cryoscopic in camphor), 330. $C_{28}H_{14}O_2N_2$ requires C, 77·65; H, 4·7%; *M*, 340]. The compound is readily soluble in cold pyridine or dioxan. Its solution in propyl alcohol yields no colour or precipitate with 2 : 4-dinitrophenylhydrazine sulphate.

6-*Methyl*-2-*tribromomethylquinoline*.—Bromination of 2 : 6-dimethylquinoline (35·0 g.) (Doebner and Miller, *Ber.*, 1883, **16**, 2465) by the method of Hammick (*J.*, 1923, 2882) yielded **6-*methyl*-2-*tribromomethylquinoline*** (54·7 g.), which separated from acetic acid as colourless narrow plates, m. p. 132—133° (Found : Br, 61·0. $C_{11}H_8NBr_3$ requires Br, 60·9%).

6-*Methyl*-2-*dibromomethylquinoline*.—The above tribromo-compound (50·0 g.) was heated at 100° with tetralin (85 ml.) for 12 hours. The mixture was diluted with light petroleum (b. p. 40—60°) and kept at 0° overnight. The light-brown crystals (24·9 g.) were recrystallised from alcohol. **6-*Methyl*-2-*dibromomethylquinoline*** was thus obtained as colourless needles, m. p. 85—86° (Found : Br, 51·0. $C_{11}H_9NBr_2$ requires Br, 50·8%).

6-*Methylquinoline*-2-*aldehyde*.—6-Methyl-2-dibromomethylquinoline (6·0 g.) was hydrolysed by means of silver nitrate (method of Hammick, *J.*, 1926, 1302). Steam-distillation from slightly alkaline solution yielded a colourless oil which solidified in the distillate. The ***aldehyde*** (2·7 g.), which was isolated by means of ether, separated from light petroleum (b. p. 40—60°) as colourless elongated plates, m. p. 105—106° (Found : C, 77·5; H, 5·3. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%).

6 : 6'-*Dimethylquinocoll* **[3 : 6-*Dihydroxy*-6' : 6''-*dimethyldiquinoline*(1' : 2' - 1 : 2)(1'' : 2'' - 4 : 5)-*pyrazinium Dihydroxide Bisanhydro-salt*]** (XXIV).—6-Methylquinoline-2-aldehyde (1·7 g.) was treated in hot aqueous alcohol with an aqueous solution of potassium cyanide (0·2 g.), and the mixture heated under reflux for 15 minutes. The reddish-brown precipitate was collected, washed with water, and crystallised several times from pyridine or dioxan. **6 : 6'-*Dimethylquinocoll*** was obtained as small slightly yellow plates, m. p. 250—251° (Found : C, 77·8; H, 4·9. $C_{28}H_{14}O_2N_2$ requires C, 77·65; H, 4·7%).

Dihydroisoquinocoll (XXI). *Action of Potassium Cyanide on* iso*Quinoline*-1-*aldehyde*.—A hot solution of isoquinoline-1-aldehyde (1·0 g.) (Barrows and Lindwall, *J. Amer. Chem. Soc.*, 1942, **64**, 2430) in aqueous alcohol (50 ml.) was treated with an aqueous solution of potassium cyanide (0·2 g.) and heated under reflux for 15 minutes. The mixture was cooled and the brown crystals (1·0 g.) were collected, washed, and dried. Several recrystallisations from alcohol yielded ***dihydroisoquinocoll*** as fine slightly brown needles, m. p. 163—164° to a dark red melt (Found : C, 76·5; H, 4·65; N, 8·9. $C_{28}H_{16}O_2N_2$ requires C, 76·4; H, 4·45; N, 8·9%). The compound shows thermochromism, its alcoholic solution passing reversibly on being heated through yellow and orange to deep red. The compound quickly reduces methylene-blue in aqueous alcohol. It yields no hydrazone with 2 : 4-dinitrophenylhydrazine sulphate in alcohol.

We thank Dr. H. M. E. Cardwell for much helpful discussion.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 5th*, 1949.]

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122. *Studies in the Polyene Series. Part XXXVI. Further Syntheses of Acetylenic Acids related to Vitamin A.*

By T. BRUUN, SIR IAN HEILBRON, B. C. L. WEEDON, and R. J. WOODS.

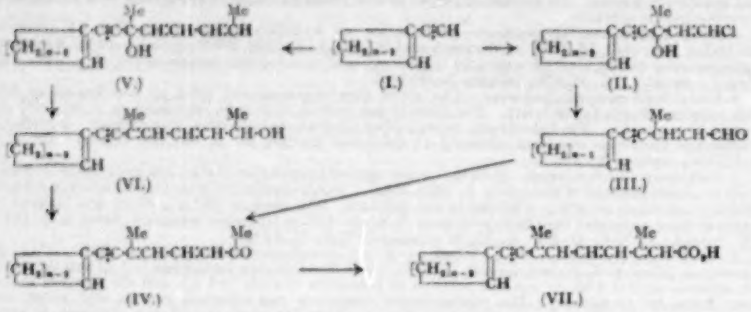
Methods previously developed for the preparation of the *cyclo*hexenyl acid (VII; $n = 6$), which possessed slight growth-promoting properties of the vitamin-A type, have now been applied to the synthesis of the *cyclo*pentenyl and *cyclo*heptenyl analogues (VII; $n = 5$ and 7), both of which were found to be biologically inactive.

As part of a general scheme for the synthesis of compounds with modified vitamin-A structures, the *cyclo*pentenyl and *cyclo*heptenyl acids (VII; $n = 5$ and 7) have now been prepared by the methods previously developed (Heilbron, Jones, and Richardson, *J.*, 1949, 287; Toogood and Weedon, *J.*, 1949, 3123) for the synthesis of the acid (VII; $n = 6$). The last was shown to possess slight but definite growth-promoting properties of the vitamin-A type, and it appeared of interest to examine the effect of varying the size of the ring system on biological activity.

The Grignard reagents from ethynyl*cyclo*pentene (I; $n = 5$) and ethynyl*cyclo*heptene (I; $n = 7$) (Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 1827) were condensed with methyl 2-chlorovinyl ketone and gave the ***carbinols*** (II; $n = 5$ and 7) in 70 and 90% yields, respectively. The latter on treatment with dilute sulphuric acid underwent anionotropic rearrangement and simultaneous loss of hydrogen chloride, yielding the ***aldehydes*** (III; $n = 5$ and 7) which were converted into the ***ketones*** (IV; $n = 5$ and 7) by condensation with acetone in the presence of aluminium *tert.*-butoxide.

The same ketones were also synthesised by the following route. The ***carbinols*** (V; $n = 5$

and 7), prepared in 65 and 60% yields, respectively, by reaction of the Grignard reagents from (I; $n = 5$ and 7) with crotonylideneacetone, were isomerised by being shaken with dilute sulphuric acid to the fully conjugated *carbinols* (VI; $n = 5$ and 7). Oppenauer oxidation of the latter furnished the ketones (IV; $n = 5$ and 7), identical with those obtained by the alternative route described above.



Condensation of the ketones (IV; $n = 5$ and 7) with methyl bromoacetate and zinc gave, after dehydration of the crude hydroxy-esters and hydrolysis, the crystalline *acids* (VII; $n = 5$ and 7), in 11 and 7% yields, respectively. Neither of these acids showed any growth-promoting properties when fed orally, as aqueous solutions of the sodium salts buffered to pH 10, to young rats deficient in vitamin A [the doses administered would have revealed activity of the same order as that of (VII; $n = 6$), *viz.*, one-thousandth of that of vitamin A itself].

The various compounds described in this paper all exhibited light-absorption properties similar to those of the corresponding *cyclo*hexenyl analogues (see table).

		$\lambda_{max.}$ A.	$\varepsilon_{max.}$			$\lambda_{max.}$ A.	$\varepsilon_{max.}$
Carbinol	(II; $n = 5$)	2290	12,000	Carbinol	(V; $n = 5$)	2280	34,500
	(II; $n = 6$) [1]	2290	13,000			2390 *	27,000
	(II; $n = 7$)	2320	17,000		(V; $n = 6$) [6]	2270	39,000
		2380 *	15,500			2370	30,000
					(V; $n = 7$)	2290	33,000
Aldehyde	(III; $n = 5$)	2270	15,500			2400 *	26,500
		3110	14,500				
	(III; $n = 6$) [1]	2230	14,000	Carbinol	(VI; $n = 5$)	2260	16,500
		2810	10,500			2830 *	21,500
		3140	14,000			2930	23,500
	(III; $n = 7$)	2260	13,000			3000 *	21,500
		3160	14,500			3080	19,000
					(VI; $n = 6$) [6]	2910	21,500
Ketone	(IV; $n = 5$)	2440	14,500			3060	15,000
		3380	28,000		(VI; $n = 7$)	2980	27,000
	(IV; $n = 6$) [6]	2450	18,000			3070 *	22,000
		3350	23,000				
	(IV; $n = 7$)	2450	13,500	Acid	(VII; $n = 5$)	2600	18,000
		3350	30,000			3400	36,000
					(VII; $n = 6$) [5]	2580	14,000
						3380	23,000
					(VII; $n = 7$)	2580	13,500
						2640	15,500
						3410	34,000

* Inflexion.

[1] Toogood and Weedon, *loc. cit.* [5] Heilbron, Jones, and Richardson, *loc. cit.* [6] Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823.

Experimental.

Light-absorption data were determined in alcohol unless stated otherwise: those not referred to below are to be found in the table. All the operations were carried out in an atmosphere of nitrogen. The 2:4-dinitrophenylhydrazones were purified by chromatographic adsorption on alumina from benzene solution.

1-Chloro-5-cyclopent-1'-enyl-3-methylpent-1-en-4-yn-3-ol (II; $n = 5$).—Ethynyl*cyclo*pentene (21 g.) (Heilbron, Jones, Toogood, and Weedon, *loc. cit.*) in ether (50 c.c.) was added dropwise to a solution

of ethylmagnesium bromide (from 5·6 g. of magnesium) in ether (100 c.c.), and the mixture was refluxed for 4 hours. After cooling, a solution of methyl 2-chlorovinyl ketone (Catch, Elliott, Hey, and Jones, *J.*, 1948, 278) (15·9 g.; freshly prepared) in ether (50 c.c.) was added during ½ hour and the mixture was refluxed for 1 hour and then cooled. The Grignard complex was decomposed with ice and ammonium chloride (20 g.) and the product was isolated with ether. Distillation gave the *carbinol* (20·9 g.) as a pale yellow viscous liquid, b. p. 65—70° (bath temp.)/10^{-4} mm., n_D^{15} 1·5398 (Found: C, 67·45; H, 6·85. $C_{11}H_{15}OCl$ requires C, 67·15; H, 6·65%).

5-cyclo*Pent*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*ol* (III; $n = 5$).—The above chloro-carbinol (26 g.) was divided into two equal portions and each was added to dilute sulphuric acid (1·5 l.; 1% w/v), and the mixtures steam-distilled. The distillates were combined and the product was isolated by ether extraction. Evaporation of the ethereal solution gave the crude aldehyde (14·7 g.) as a yellow oil, n_D^{15} 1·5791. Light absorption: maxima, 3080 and 3170 A.; $E_{1cm}^{1\%}$, 780 and 730, respectively, indicating a purity of *ca.* 80%. The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate–methanol in dark red needles, m. p. 164—165° (Found: N, 16·7. $C_{17}H_{16}O_4N_4$ requires N, 16·45%). Light absorption in chloroform (main band only): maximum, 3940 A.; ε, 36,000.

The crude aldehyde (5 g.) was treated with an excess of semicarbazide acetate in aqueous methanol (80%) and gave the *semicarbazone* (2·5 g.), which crystallised from alcohol in plates, m. p. 206—207° (decomp.) (Found: N, 19·3. $C_{12}H_{15}ON_3$ requires N, 19·35%). Light absorption: maxima, 2450 and 3160 A.; ε, 11,500 and 30,500, respectively. Inflexion, 3300 A.; ε, 21,000. A mixture of the semicarbazone (1·6 g.), dilute sulphuric acid (50 c.c.; 10% w/v), and light petroleum (50 c.c.; b. p. 80—100°) was refluxed with vigorous stirring for 4 hours. After removal of unreacted semicarbazone (0·8 g.), the petroleum layer was separated, washed with water, dried, and evaporated. Distillation of the residue gave 5-cyclo*pent*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (0·3 g.) as a yellow viscous liquid, b. p. 60° (bath temp.)/10^{-4} mm., n_D^{15} 1·5830, which crystallised when kept at 0° (Found: C, 83·0; H, 7·85. $C_{11}H_{12}O$ requires C, 82·45; H, 7·55%).

1-cyclo*Pent*-1′-*enyl*-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (V; $n = 5$).—Crotonylideneacetone (14·4 g.) in ether (20 c.c.) was added during 1 hour to a cooled suspension of *cyclo*pentenylethynylmagnesium bromide (prepared as described above from 3·2 g. of magnesium and 12·1 g. of ethynylcyclopentene) in ether (500 c.c.). After the mixture had been stirred at 20° for 1 hour, the complex was decomposed by addition of ice and ammonium chloride (20 g.). Isolation gave the *carbinol* (17·3 g.) as a pale yellow liquid, b. p. 75—80° (bath temp.)/10^{-4} mm., n_D^{15} 1·5465 (Found: C, 83·1; H, 9·0. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

8-cyclo*Pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (VI; $n = 5$).—A mixture of the carbinol (V; $n = 5$) (4·8 g.), dilute sulphuric acid (250 c.c.; 1% w/v), ether (50 c.c.), and a trace of quinol was shaken at 20° for 18 hours. The ethereal layer was separated, washed well with water, dried, and evaporated. Distillation of the residue gave the rearranged *carbinol* (2·3 g.) as a yellow oil, b. p. 80—85° (bath temp.)/10^{-4} mm., n_D^{15} 1·5882 (Found: C, 82·85; H, 9·1. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

8-cyclo*Pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (IV; $n = 5$).—(*a*) A solution of the aldehyde (III; $n = 5$) (14·7 g.; crude) and aluminium *tert.*-butoxide (20·6 g.) in a mixture of acetone (400 c.c.) and benzene (675 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (1200 c.c.; 2·5% w/v), and the organic layer separated. The aqueous solution was extracted with ether and the combined ethereal extracts and benzene layer was washed with sodium hydrogen carbonate solution and water and dried. Evaporation of the solvents and distillation of the residue (9·3 g.) gave the crude ketone (5·5 g.), b. p. 85—90° (bath temp.) 10^{-4} mm., n_D^{15} 1·6064. Light absorption: maxima, 2400 and 3300 A.; $E_{1cm}^{1\%}$, 470 and 800, respectively. Inflexion, 3480 A.; $E_{1cm}^{1\%}$, 680, indicating a purity of *ca.* 45—50%. The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate in needles and pyramids, m. p. 218—219°. The former were converted into the latter on keeping in contact with solvent and on heating (Found: N, 14·85. $C_{20}H_{20}O_4N_4$ requires N, 14·75%). Light absorption in chloroform (main band only): maximum, 4050 A.; ε, 47,500.

The crude ketone (0·6 g.) was treated with an excess of semicarbazide acetate in aqueous methanol and gave the *semicarbazone* (0·26 g.), which crystallised from methanol in needles, m. p. 169—170° (decomp.) (Found: N, 16·15. $C_{15}H_{19}ON_3$ requires N, 16·35%). Light absorption: maxima, 2640 and 3330 A.; ε, 16,500 and 47,000, respectively. A mixture of the semicarbazone (0·4 g.), dilute sulphuric acid (20 c.c.; 10% w/v), and light petroleum (20 c.c.; b. p. 80—100°) was refluxed with vigorous stirring until all the solid had disappeared (15 minutes). Isolation gave 8-cyclo*pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (0·17 g.) as a yellow viscous oil, b. p. 70° (bath temp.)/10^{-4} mm., n_D^{15} 1·6179, which crystallised when kept at 0° (Found: C, 84·05; H, 8·4. $C_{14}H_{14}O$ requires C, 83·95; H, 8·05%).

(*b*) A solution of the carbinol (VI; $n = 5$) (1·4 g.) and aluminium *tert.*-butoxide (4 g.) in a mixture of benzene (10 c.c.) and acetone (60 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (460 c.c.; 2·5% w/v), and the product isolated. Distillation gave the crude ketone (1·1 g.), n_D^{15} 1·5920. Light absorption: maxima, 2280, 2420, 3330, and 3380 A.; $E_{1cm}^{1\%}$, 550, 550, 710, and 680, respectively. Inflexion, 3200 A.; $E_{1cm}^{1\%}$, 680. The 2:4-dinitrophenylhydrazone crystallised from ethyl acetate in needles and pyramids, m. p. 218—219°, undepressed on admixture with a specimen from (*a*). The semicarbazone crystallised from methanol in needles, m. p. 169—170° (decomp.), undepressed on admixture with a specimen from (*a*).

8-cyclo*Pent*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VII; $n = 5$).—A mixture of the ketone (IV, $n = 5$) [4 g.; crude, from (*a*)], methyl bromoacetate (3·5 g.), activated zinc turnings (1·3 g.), a trace of mercuric chloride, and benzene (70 c.c.) was refluxed for ½ hour, all the zinc having then dissolved. The deep-red mixture was cooled and shaken with dilute acetic acid (125 c.c.; 5%). The benzene layer was washed free from acid, dried, and evaporated, giving a mixture (4·5 g.) of hydroxy- and unsaturated esters. Light absorption: maxima, 2820 and 2920 A.; $E_{1cm}^{1\%}$, 620 and 620. Inflexion, 3000 A.; $E_{1cm}^{1\%}$, 530. Anhydrous oxalic acid (15 g.) was added and the mixture was heated at 95—100° (bath temp.)/10·1 mm. for 2 hours. After cooling, the crude unsaturated ester was isolated by extraction

with light petroleum (b. p. 40—60°). Light absorption: maxima, 2600 and 3450 A.; $E^{1\%}_{1cm.}$, 370 and 800, respectively.

The *ester* was dissolved in methanolic potassium hydroxide (150 c.c.; 10% w/v), and the solution kept at 20° for 64 hours. The solution was poured into water (500 c.c.), the non-hydrolysable material extracted with ether, and the aqueous layer acidified with phosphoric acid (50 c.c.; 50% w/v). The liberated acid was extracted with ether and the ethereal solution was washed with water, dried, and evaporated. Recrystallisation of the residue from methanol gave the *acid* (270 mg.), m. p. 185—186° (Found: C, 79·5; H, 8·0. $C_{16}H_{16}O_3$ requires C, 79·3; H, 7·5%).

1-*Chloro*-5-cyclo*hept*-1′-*enyl*-3-*methylpent*-1-*en*-4-*yn*-3-*ol* (II; n = 7).—Ethynylcycloheptene (24 g.) (*loc. cit.*) was condensed with methyl 2-chlorovinyl ketone (11·5 g.) by the procedure described above for the *cyclo*pentenyl analogue. Distillation of the product gave: (i) recovered ethynylcycloheptene (9·5 g.); (ii) the *carbinol* (21 g.) as a pale yellow viscous oil, b. p. 80—85° (bath temp.)/10^{-4} mm., n_D^{18} 1·5372 (Found: C, 69·05; H, 7·7. $C_{15}H_{17}OCl$ requires C, 69·5; H, 7·6%).

5-cyclo*Hept*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*ol* (III; n = 7).—The chloro-carbinol (II; n = 7) (20 g.) was divided into two equal portions and each was added to dilute sulphuric acid (1 l.; 1% w/v) and the mixtures steam distilled. The distillates were combined and the product was isolated with ether and distilled, giving the crude aldehyde (10 g.), b. p. 80° (bath temp.)/10^{-4} mm., n_D^{18} 1·5716. Light absorption: maxima, 2270 and 3150 A.; $E^{1\%}_{1cm.}$, 580 and 560, respectively, indicating a purity of *ca.* 70%. The *semicarbazone* crystallised from methanol in plates, m. p. 205° (Found: N, 17·0. $C_{16}H_{19}ON_3$ requires N, 17·1%). Light absorption: maxima, 2410 and 3170 A.; ε, 12,500 and 29,500, respectively. The 2:4-*dinitrophenylhydrazone* crystallised from light petroleum (b. p. 60—80°) in dark-red plates, m. p. 156° (Found: N, 15·4. $C_{20}H_{20}O_4N_4$ requires N, 15·2%). Light absorption in chloroform (main band only): maximum, 3980 A.; ε, 39,000.

A mixture of the semicarbazone (1 g.), dilute sulphuric acid (30 c.c.; 10% w/v), and light petroleum (30 c.c.; b. p. 80—100°) was stirred vigorously under reflux until all the solid had disappeared (5 hours). Isolation of the product gave the *aldehyde* (0·5 g.) as a pale yellow oil, b. p. 80° (bath temp.)/10^{-4} mm., n_D^{18} 1·5700 (Found: C, 82·7; H, 9·15. $C_{15}H_{16}O$ requires C, 82·9; H, 8·55%).

1-cyclo*Hept*-1′-*enyl*-3-*methylocta*-4:6-*dien*-1-*yn*-3-*ol* (V; n = 7).—Crotonylideneacetone (14·5 g.) in ether (25 c.c.) was added during ½ hour to a cooled suspension of *cyclo*heptenylethynylmagnesium bromide (prepared from 3·0 g. of magnesium and 15·0 g. of ethynylcycloheptene) in ether (500 c.c.). After the mixture had been stirred at 20° for 1 hour, the complex was decomposed and the product was isolated and distilled, giving the *carbinol* (18·0 g.), b. p. 85—95° (bath temp.)/10^{-4} mm., n_D^{18} 1·5430 (Found: C, 83·45; H, 10·0. $C_{16}H_{22}O$ requires C, 83·45; H, 9·6%).

8-cyclo*Hept*-1′-*enyl*-6-*methylocta*-3:5-*dien*-7-*yn*-2-*ol* (VI; n = 7).—A solution of the preceding carbinol (15·0 g.), and a trace of quinol, in ether (50 c.c.) was shaken for 15 hours with dilute sulphuric acid (900 c.c.; 0·5% w/v). Isolation of the product gave the crude carbinol. Distillation, which was accompanied by extensive polymerisation, yielded the *carbinol* (8·0 g.) as a viscous pale yellow oil, b. p. 90—100° (bath temp.)/10^{-4} mm., n_D^{18} 1·5800 (Found: C, 83·4; H, 9·9. $C_{16}H_{22}O$ requires C, 83·45; H, 9·6%).

8-cyclo*Hept*-1′-*enyl*-6-*methylocta*-3:5-*dien*-7-*yn*-2-*one* (IV; n = 7).—(*a*) A solution of the aldehyde (III; n = 7) (18 g.; crude) and aluminium *tert.*-butoxide (25 g.) in a mixture of benzene (800 c.c.) and acetone (400 c.c.) was refluxed for 48 hours. Isolation of the product and distillation gave the ketone (14 g.) as an oil, b. p. 100—110° (bath temp.)/10^{-4} mm., n_D^{18} 1·5920. Light absorption: maxima, 2280, 2370, 2800, and 3300 A.; $E^{1\%}_{1cm.}$, 510, 620, 420, and 770, respectively, indicating a purity of *ca.* 85—90%. The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark-red plates, m. p. 200° (Found: N, 13·8. $C_{22}H_{24}O_4N_4$ requires N, 13·7%). Light absorption in chloroform (main band only): maximum, 4080 A.; ε, 36,000. The *semicarbazone*, which formed slowly and in poor yield, crystallised from ethanol in pale yellow needles, m. p. 181° (Found: C, 71·55; H, 8·1. $C_{17}H_{23}ON_3$ requires C, 71·55; H, 8·1%). Light absorption: maximum, 3360 A.; ε, 42,500. Inflexion, 3480 A.; ε, 31,500.

A portion (0·8 g.) of the crude ketone was dissolved in light petroleum (b. p. 40—60°) and the solution was poured on a column of partially deactivated alumina (100 g.; Grade IV, *cf.* Brockmann and Schodder, *Ber.*, 1941, **74**, 73). The chromatogram was developed with the same solvent and the yellow band formed was eluted and collected in two fractions. Removal of the solvent under reduced pressure and distillation of the residues gave: (i) (least strongly adsorbed) an oil (0·35 g.), b. p. 110—120° (bath temp.)/10^{-4} mm., n_D^{18} 1·5920, and (ii) the *ketone* (0·4 g.) as a pale yellow oil, b. p. 110—120° (bath temp.)/10^{-4} mm., n_D^{18} 1·6132 (Found: C, 84·2; H, 9·2. $C_{16}H_{20}O$ requires C, 84·15; H, 8·85%).

(*b*) A solution of the carbinol (VI; n = 7) (9·0 g.) and aluminium *tert.*-butoxide (12·5 g.) in a mixture of acetone (250 c.c.) and benzene (420 c.c.) was refluxed for 48 hours. Isolation gave the crude ketone (7·0 g.) as a pale yellow oil, b. p. 100—110° (bath temp.)/10^{-4} mm.; n_D^{18} 1·5840. Light absorption: maxima, 2450, 3160, and 3370 A.; $E^{1\%}_{1cm.}$, 560, 720, and 720, respectively, indicating an appreciable content of the required ketone.

A solution of the crude ketone (7·0 g.) and Girard reagent-T (7·0 g.) in acetic acid (7·5 c.c.) and alcohol (70 c.c.) was refluxed for 1 hour. Distillation of the crude ketonic material isolated in the usual manner gave the ketone (4 g.), b. p. 90—100° (bath temp.)/10^{-4} mm., n_D^{17} 1·6039. The 2:4-dinitrophenylhydrazone crystallised from ethyl acetate in dark red plates, m. p. 199°, undepressed on admixture with a specimen from (*a*). The semicarbazone, which formed slowly and in poor yield, crystallised from methanol in needles, m. p. 179°, undepressed on admixture with a specimen from (*a*).

8-cyclo*Hept*-1′-*enyl*-2:6-*dimethylocta*-1:3:5-*trien*-7-*yne*-1-*carboxylic Acid* (VII; n = 7).—The ketone (IV; n = 7) [6·0 g. crude, prepared by route (*a*) above] in benzene (120 c.c.) was condensed with ethyl bromoacetate (5·3 g.) and zinc (1·9 g.). The resulting crude hydroxy-ester was dehydrated, giving the crude unsaturated ester (8·5 g.), n_D^{18} 1·572. Light absorption: maxima, 2490, 2800, and 3420 A.; $E^{1\%}_{1cm.}$, 540, 370, and 680, respectively.

The unsaturated ester was dissolved in a solution of potassium hydroxide in methanol (250 c.c.;

10% w/v), and the solution kept at 20° for 96 hours. Isolation of the acid fraction yielded a viscous yellow gum which partly solidified on trituration with ether. Recrystallisation of the solid from methanol gave the *acid* (0·5 g.) as needles, m. p. 181° (Found: C, 79·8; H, 8·55. $C_{13}H_{16}O_3$ requires C, 79·05; H, 8·2%).

A sample of the ketone (IV; n = 7), prepared by route (*b*) above, was also converted into the acid, which crystallised from methanol in needles, m. p. 181°, undepressed on admixture with the specimen described above.

The authors are indebted to the Rockefeller Foundation for financial assistance and to Glaxo Laboratories Ltd. for biological assays. One of them (T. B.) thanks the Norges Tekniske Högskole for a grant, and another (R. J. W.) thanks the Ministry of Education for a Royal Scholarship. Light-absorption data were determined by Dr. E. A. Braude.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
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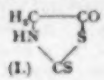
123. *Studies in the Azole Series. Part XXV. The Action of Bases on 2-Thio-5-thiazolidone.*

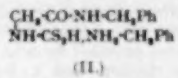
By A. H. COOK and A. L. LEVY.

2-Thio-5-thiazolidone (I) reacts vigorously with primary and secondary bases to give salts of the corresponding *N*-dithiocarboxyglycine amides (*e.g.*, II). In the presence of aqueous acids these are recyclised to (I), but with anhydrous acids afford carbon disulphide and the corresponding glycine amide salts. Triethylamine or aqueous alkali causes dimerisation of (I) to a derivative of diaminoacetone, whereas pyridine and alcohols effect polymerisation to polyglycines of low molecular weight.

IN Part III (Cook, Heilbron, and Levy, *J.*, 1948, 201) a synthesis of the novel 2-thio-5-thiazolidone (I) by the action of acids on salts of carbamylmethyldithiocarbamic acid was described. The present communication is concerned with a study of the action of bases on this compound (I).



(I.)



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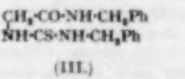
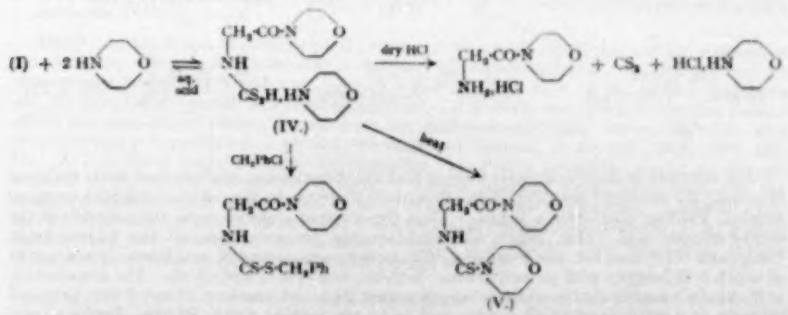


(III.)

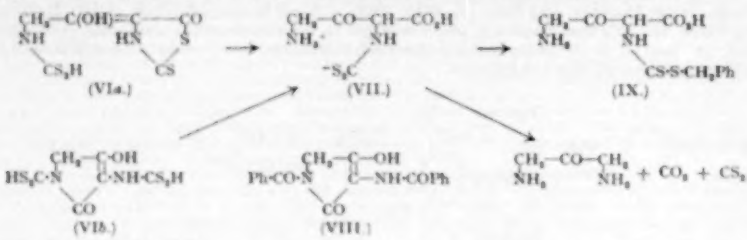
When (I) was treated with benzylamine in ether at 0°, the product rapidly separated as a gum, which was presumably benzylammonium *N*-(*N'*-benzylcarbamylmethyl)dithiocarbamate (II), since it readily regenerated (I) on acidification. Dissolved in benzylamine, however, and gently warmed, (I) yielded the crystalline thiourea (III), identical with that described earlier (Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1058). It will be recalled (Cook, Harris, Heilbron, and Shaw, *loc. cit.*) that relatively minor changes in the experimental conditions gave either (III) or benzyl *N*-(*N'*-benzylcarbamidomethyl)dithiocarbamate, when 2-benzylthio-5-thiazolinone was treated with benzylamine.



Morpholine, selected as a model secondary amine, was found to react rapidly and exothermally with (I) in ether, acetone, or ethanol to give the *morpholinium* salt of *N*-dithiocarboxy-

glycine morpholide (IV) in a yield of 87%. This structure was confirmed by shaking (IV) with benzyl chloride in ether–water, whereupon the S-*benzyl* ester was produced. Under more vigorous conditions, however, or when (IV) was heated in methanol, hydrogen sulphide was lost and the substituted *thiourea* (V) was produced. (IV) was reconverted into (I) in 84% yield by dissolution in water and acidification with hydrochloric acid, so that the synthesis of the thiothiazolidone is by no means confined to simple carbamylalkyldithiocarbamates. Indeed, the morpholide (IV) appeared to undergo cyclisation even more readily than the simple amide. When (IV) was treated with dry hydrogen chloride in chloroform, however, another reaction took place, carbon disulphide, morpholine hydrochloride, and *glycine morpholide hydrochloride* being produced. When 3-acetyl-2-thio-5-thiazolidone (Cook, Heilbron, and Levy, *loc. cit.*) (the location of the acetyl group in the 3-position is not proven though it is supported by the low melting point of the compound) was treated with morpholine in acetone, (IV) was once again produced; the acetyl group was also detached by rapid treatment with warm concentrated hydrochloric acid, (I) being isolated.

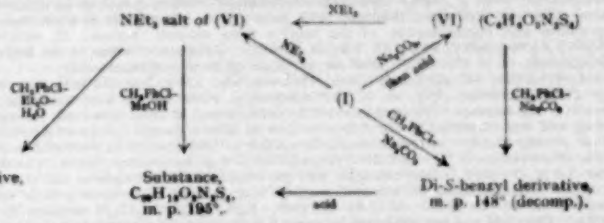
When 2-thio-5-thiazolidone (I) was treated with triethylamine in acetone, a crystalline *salt* rapidly separated which seemed from its composition to be the triethylamine salt of (I). On acidification in water, however, it gave a labile yellow isomeride of (I), which for reasons which will now be developed is regarded as a *dimeride*, $C_6H_6O_2N_2S_4$ (VI). This substance was soluble in sodium hydrogen carbonate and gave a dark green colour with ferric chloride. The same compound was produced, to the extent of about 60%, by keeping (I) overnight in sodium hydroxide or carbonate solution, and acidifying the solution; the remaining 40% was converted into sodium carboxymethyldithiocarbamate, which decomposed to give glycine and carbon disulphide on acidification. The dimeride was freely soluble in cold acetone, methanol, or ethanol, but after a few minutes these solutions deposited colourless needles of a compound, $C_6H_6O_2N_2S_4$ (VII), which was soluble in sodium hydroxide though no longer soluble in sodium hydrogen carbonate, and gave a deep green colour, rapidly becoming purple, with ferric chloride. It afforded a reddish-purple colour with the ninhydrin reagent, was insoluble in common solvents, and melted with decomposition about 200°. Inspection of the empirical formula shows that loss of carbon disulphide and addition of the elements of water had occurred in this reaction. The compound (VII) was most conveniently prepared by dissolving the triethylamine salt of (VI) in acetic acid, whereupon it separated almost immediately in 75% yield. An important clue to the nature of these compounds was provided by acid hydrolysis of (VII), which very readily gave carbon disulphide, carbon dioxide, and 1 : 3-diaminoacetone (isolated as its *dipicrate*). The dimeride (VI) also yielded these products when boiled for a short while with 2*N*-hydrochloric acid, but a sulphur-containing *substance* isomeric with (VII), but of unknown structure, was formed in addition. The last-mentioned substance gave no diaminoacetone on further hydrolysis, and therefore represents an alternative path of decomposition.



The isolation of diaminoacetone showed that the dimerisation reaction essentially involved attaching the carbonyl grouping of one thiazolone molecule to the active methylene group of another, yielding ultimately a ketone. Thus the simplest expression for the dimeride is the dithiocarbamic acid (VIa), which also satisfactorily accommodates all the known facts. Compound (VII) then becomes *γ-amino-α-dithiocarboxyaminoacetoacetic acid betaine*, the structure of which is in keeping with its zwitterionic character and ease of hydrolysis. The dimerisation of (I) recalls a similar change which takes place when 2-phenyloxazolone is treated with Grignard reagents or a mixture of triethylamine and hydrogen cyanide (Cook, Elvidge, Heilbron, and Levy, "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 738; Bailey, Baker, and Bradley, *ibid.*). The dimeride in this case has been shown to be "dibenzamidodi-

oxytetrol" (VIII) (Cornforth and Huang, *J.*, 1948, 1958), and so the formally similar expression (VIb) should be considered for the dimeride of 2-thio-5-thiazolidone. This alternative expression would not seem to account so well, however, for the addition of water under mild conditions to give (VII).

When (VII) was shaken with benzyl chloride and sodium carbonate solution a mono-*S*-benzyl derivative was obtained, which formed a highly crystalline *hydrochloride*. It was soluble in aqueous sodium hydroxide (though not in aqueous sodium carbonate) and gave an intense colour with the ninhydrin reagent, even in the presence of cupric carbonate, and is therefore formulated as the γ-amino-acid (IX). Under other conditions (I), (VI), and the triethylamine salt of (VI) give altogether three further benzyl *derivatives*; the analyses, solubilities in alkali, and colour reactions do not, however, provide sufficient evidence on which to assign structures to them, but their interrelations are summarised in the following scheme:



Acetylation of (I), (VI), and (VII) in the presence of bases leads to a variety of derivatives dependent on quite small changes in the experimental conditions. The products contain either 2 or 3 acetyl groups, and have all to some extent lost the elements of water. While it is yet too soon to assign individual structures, it is probable from the fact that they do not give ferric chloride colours and do not regenerate the starting materials on hydrolysis, that the products are acetylated thiazoles and oxazoles formed by cyclisation of $-NH\cdot CS_2H$ and $-NH\cdot CO\cdot CH_2$ on to the enolic hydroxyl group of (VI) and (VII). The results are summarised in the table.

Starting material.	Reagent.	Derivative of (VI) produced. No. of Ac groups.	Elements lost.	M. p.
(I)	Ac_2O–NEt_3			
(VI) [a]	Ac_2O + trace of NEt_3	3	H_2O	137°
"	Ac_2O–C_5H_5N	—	—	95
"	Ac_2O–NEt_3	2	CS_2, H_2O	158
NEt_3 derivative [b] of (VI)	Ac_2O			
NEt_3 derivative [c] of (VII)	Ac_2O–NEt_3	3	$2H_2O$	147
" " "	Ac_2O–C_5H_5N	—	—	173

[a] From (I) by aqueous alkali. [b] From (I) by NEt_3. [c] From (VI) by pyridine or from the NEt_3 derivative of (VI) by AcOH.

Finally, by the action of pyridine on (I), slowly in the cold or rapidly on heating, a *substance* was produced which was insoluble in water and all organic solvents, and soluble only in concentrated hydrochloric acid and aqueous alkalis. Since most of the sulphur had been lost, the material is regarded as a crude polyglycine. It is worth recalling that pyridine rapidly effects the expulsion of carbon dioxide from the analogous anhydrocarboxyamino-acids, with accompanying polymerisation (*inter alia*, Wesseley and Sigmund, *Z. physiol. Chem.*, 1926, **157**, 91). A Van Slyke amino-nitrogen determination indicated a molecular weight of 605 per terminal $-NH_2$, which corresponds to about 9 glycine residues, in fair agreement with the analytical figures, which indicate one atom of sulphur in such a molecule. Insoluble high-melting substances of similar gross composition were also produced by refluxing (I) for a short time in methanol or ethanol, the methoxyl content of a product from the former solvent indicating an average molecular length of 8 glycine residues.

Experimental.

Action of Benzylamine on (I).—2-Thio-5-thiazolidone (1·0 g.) was dissolved in dry ether, and benzylamine (1·61 g., 2 equivs.) added at 0°. A white solid separated at once, which became gummy on exposure to air and afforded (I) on acidification with 2*N*-hydrochloric acid.

Action of Morpholine on (I).—Morpholine (1·8 g., 2 equivs.) was added to 2-thio-5-thiazolidone (1·3 g.) in acetone (20 c.c.) at 0° during 2 minutes, and the product (2·6 g., 87%), m. p. 127° (decomp.), filtered off after 15 minutes at room temperature. The *morpholinium* salt of *N*-dithiocarboxyglycine-morpholide (IV) recrystallised from aqueous acetone in rectangular prisms, m. p. 142° (decomp.) (Found: C, 43·4; H, 6·4; N, 13·6. $C_{11}H_{18}O_3N_2S_3$ requires C, 43·0; H, 6·8; N, 13·7%), though after crystallisation from hot methanol the m. p. rose to 193°, giving (V). It gave a colourless precipitate with aqueous mercuric chloride, a creamy precipitate (decomp. 100°) with lead acetate, and a pale yellow silver salt which rapidly darkened and was black after 1—2 minutes. The salt (IV) was shaken with excess of benzyl chloride in ether–water for 2·5 hours, whereupon the *benzyl* ester separated; it recrystallised from ethanol in star-like clusters of needles, m. p. 135—136° (Found: C, 54·2; H, 6·1; N, 8·8. $C_{14}H_{18}O_3N_2S_3$ requires C, 54·2; H, 5·8; N, 9·0%). (I) (1·3 g.) was warmed on the steam-bath with morpholine (10 c.c.) for 5 minutes and diluted with acetone to give the substituted *thiourea* (V) (0·7 g.), m. p. 195—196° (decomp.) (after crystallisation from methanol or water) (Found: N, 15·5. $C_{11}H_{18}O_3N_4S$ requires N, 15·4%).

The salt (IV) (2·6 g.) in water (10 c.c.) was treated with concentrated hydrochloric acid (3 c.c.) at 0°, whereupon (I) (0·95 g., 84%) separated immediately. When dissolved in chloroform, however, and treated with dry hydrogen chloride, (IV) gave *glycine morpholide hydrochloride*, m. p. 238°, after evaporation and crystallisation of the residue from ethanol (Found: C, 40·8; H, 7·2; N, 14·9. $C_6H_{13}O_3N_2Cl$ requires C, 39·9; H, 7·2; N, 15·5%). Addition of ether to the filtrate gave morpholine hydrochloride, m. p. 178—179° (after recrystallisation from methanol–ether).

3-Acetyl-2-thio-5-thiazolidone (Cook, Heilbron, and Levy, *loc. cit.*) with morpholine in acetone or ethyl acetate afforded (IV), m. p. 137° (decomp.), when seeded and scratched. When the acetyl derivative was warmed with concentrated hydrochloric acid until dissolved, (I) separated in flakes on cooling, and was identified by its ability to give an intense purple colour with iodine in the presence of sodium acetate and by the characteristic formation of long needles on recrystallisation from benzene.

The Dimerisation of (I).—2-Thio-5-thiazolidone (1·3 g.) in acetone (15 c.c.) was treated with triethylamine (1·0 g., 1 equiv.) under nitrogen, and the resulting *bistriethylamine* salt (1·4 g., 61%), m. p. 133° (decomp.), collected after 20 minutes, washed with acetone to remove a little colour, and analysed directly (Found: C, 46·55; H, 7·9; N, 11·9. $C_3H_4O_2N_2S_4,2C_6H_{15}N$ requires C, 46·1; H, 7·7; N, 11·9%). The yield was not improved by using 2 equivalents of triethylamine. It was soluble in water, methanol, chloroform, or pyridine, insoluble in ethanol, ether, or ethyl acetate, and was best recrystallised from methanol–ethyl acetate. The triethylamine salt was unstable, changing to a black tar when kept overnight, and solutions rapidly developed intense red and purple colours on exposure to air. Treatment with morpholine in chloroform caused separation of the corresponding morpholine salt, m. p. 154° (decomp.).

When the triethylamine salt was dissolved in water and acidified with concentrated hydrochloric acid at 0°, a yellow gum was precipitated which solidified after a little scratching to give the dimeride (see below). Conversely, the triethylamine or morpholine salt was obtained, when this was treated with the appropriate base in acetone. The *dimeride* (VI) (4·5 g., 64%) was best prepared by keeping (I) (7·0 g.) in 10% sodium hydroxide solution (40 c.c.) overnight under nitrogen and then acidifying the solution at 0° (Found: C, 27·4; H, 2·4; S, 47·7. $C_6H_4O_2N_2S_4$ requires C, 27·1; H, 2·3; S, 48·1%); carbon disulphide was present in the filtrate. The same results were obtained using sodium carbonate solution. Thus secured, the dimeride darkened gradually at >200°, obvious decomposition setting in at >250°. It was soluble in aqueous sodium hydrogen carbonate with effervescence, the solution darkening if exposed to air, and was precipitated unchanged on acidification. It was insoluble in benzene, ethyl acetate, ether, or chloroform, but freely soluble in cold acetone or methanol, and rather less so in ethanol.

When kept for 5—10 minutes, or immediately when boiled or treated with pyridine, the above solutions deposited the *betaine* (VII) which decomposed indefinitely above 200°, was insoluble in all common solvents, and could be recrystallised from a large volume of water in long, colourless needles (Found: C, 29·3; H, 4·2; N, 13·0; S, 30·6. $C_6H_4O_2N_2S_3$ requires C, 28·9; H, 3·9; N, 13·5; S, 30·8%). The compound was soluble in aqueous sodium hydroxide, whence it was reprecipitated by acids, difficultly soluble in sodium carbonate, and insoluble in sodium hydrogen carbonate. The compound was most conveniently prepared by dissolving the triethylamine salt of (VI) (4·2 g.) in acetic acid (25 c.c.) under nitrogen, and collecting the crystals (1·4 g., 75%) after 0·5 hour.

Acid Hydrolyses.—The above compound (VII) (0·5 g.) was heated under reflux with 2*N*-hydrochloric acid (10 c.c.) for 3 minutes, by which time a clear solution had resulted. Carbon disulphide was observed as oily drops in the condenser, and carbon dioxide was detected with saturated aqueous barium hydroxide in the usual way. Evaporation gave diaminoacetone dihydrochloride which was not readily purified but with picric acid yielded 1 : 3-*diaminoacetone dipicrate* which crystallised from dilute aqueous picric acid in long yellow needles, m. p. 210—215° (decomp.) (Found: C, 31·9; H, 3·0. $C_3H_4ON_2,2C_6H_3O_7N_3,H_2O$ requires C, 31·9; H, 2·9%). The same dipicrate was prepared from authentic diaminoacetone, obtained by hydrolysis of "dibenzamidodioxytetrol" (Rügheimer, *Ber.*, 1888, **21**, 3325). The betaine (VII) was also decomposed by boiling it with water for 15 minutes, but addition of picric acid failed to yield the above picrate in this case.

The dimeride (VI) (1·5 g.) was heated under reflux with 2*N*-hydrochloric acid (10 c.c.) for 10 minutes, dissolving with vigorous effervescence (carbon dioxide) and production of carbon disulphide. The solution was evaporated, and the yellow gum dissolved in water (8 c.c.), granular prisms (0·5 g.), m. p. 177° (decomp.), being slowly deposited; the filtrate gave diaminoacetone dipicrate (0·25 g.) with picric acid. The above *substance* was recrystallised from water containing a little hydrochloric acid, whence it separated slowly and had m. p. 174° (decomp.) (Found: C, 29·3, 28·6; H, 4·3, 3·7; N, 14·6, 12·5. $C_4H_4O_2N_2S_2$ requires C, 28·9; H, 3·9; N, 13·5%). It was sparingly soluble in common solvents, soluble in aqueous sodium hydroxide though not in sodium hydrogen carbonate and was recovered unchanged after being heated for 0·5 hour at 100° with 2*N*-hydrochloric acid. The dimeride (VI) was transformed in poor yield into (VII) when boiled with water.

Benzylation Experiments.—Compound (VII) (0·77 g.) was suspended in 2*N*-sodium carbonate (10 c.c.)

and shaken overnight with benzyl chloride (2 c.c.) and ether (10 c.c.). The insoluble benzyl derivative (0·64 g.), m. p. 180° (decomp.), was recrystallised from 2*N*-hydrochloric acid as its *hydrochloride*, in colourless needles, m. p. 194—195° (decomp.) (Found: C, 43·8; H, 4·4; N, 8·3; Cl, 11·0. $C_{11}H_{14}O_4N_2S_2$,HCl requires C, 43·1; H, 4·5; N, 8·4; Cl, 10·6%). It was soluble in methanol and insoluble in acetone, and gave a green colour with ferric chloride in methanol. If insufficient acid was present during the recrystallisation, the free base, m. p. 178° (decomp.), separated, insoluble in methanol and hot water, though soluble in hot sodium carbonate solution and cold sodium hydroxide solution. The amino-acid, when heated with ninhydrin and sodium acetate, gave a reddish colour becoming intense green in the presence of cupric carbonate. DL-Alanine gave no colour under these conditions.

2-Thio-5-thiazolidone (I) (5·0 g.) in 2*N*-sodium carbonate (50 c.c.) was shaken overnight with benzyl chloride (5 c.c.) in ether (30 c.c.) under nitrogen; an insoluble *S*-benzyl derivative (4·0 g.), m. p. 148° (decomp.), was produced. Acidification of the aqueous layer gave *N*-dithiocarbobenzyloxyglycine (1·2 g.), m. p. 164°. The benzyl derivative was soluble in acetone and ethyl acetate, sparingly soluble in cold methanol or ethanol, and insoluble in ether, chloroform, or light petroleum; it decomposed in hot solvents. The same compound (1·2 g.) was produced when (VI) (1·0 g.) in 2*N*-sodium carbonate (20 c.c.) was shaken with benzyl chloride (1·5 c.c.) in ether for 1·5 hours under nitrogen. In acetone, it gave a deep indigo-blue colour with ferric chloride, extractable into chloroform, which became green with excess of ferric chloride.

When the preceding benzyl derivative was crystallised rapidly from hot acetic acid, a *compound* separated in needles, m. p. 195° (decomp.) (Found: C, 53·9; H, 4·2; N, 6·5; S, 28·3. $C_{18}H_{18}O_3N_2S_4$ requires C, 53·8; H, 4·0; N, 6·3; S, 28·7%). The acidity of the acetic acid was responsible for this change, which was more conveniently effected by adding a few drops of concentrated hydrochloric acid to an acetone solution of the lower-melting benzyl derivative, whereupon the compound, m. p. 195°, was quantitatively precipitated. It was insoluble in common solvents, and gave a deep green colour when warmed with methanolic ferric chloride. Both benzyl derivatives were insoluble in cold 2*N*-sodium hydroxide, but dissolved on heating, with liberation of toluene-α-thiol; acidification gave a yellow flocculent precipitate. When the triethylamine salt of (VI) was warmed with benzyl chloride in methanol or chloroform, the benzyl derivative, m. p. 195° (decomp.), rapidly separated. When shaken overnight with benzyl chloride (3 c.c.) in ether (10 c.c.) and water (8 c.c.), however, the triethylamine salt (2·6 g.) yielded a different benzyl derivative (1·9 g.), m. p. 140° (decomp.). This was unaffected by cold dilute acids, but was soluble in cold 2*N*-sodium hydroxide liberating triethylamine, whereafter acidification afforded a yellow precipitate, m. p. 110° (decomp.) after contracting at 76°.

Acetylation Experiments.—The bistriethylamine salt of (VI) was warmed with excess of acetic anhydride for a few minutes, cooled, scratched, and diluted with water to give a *diacetyl* derivative, m. p. 157—158°, colourless needles from ethanol (Found: C, 40·5; H, 2·9; N, 10·7; S, 25·5. $C_8H_8O_4N_2S_2$ requires C, 42·2; H, 3·1; N, 10·9; S, 25·0%). The compound was insoluble in cold 2*N*-sodium hydroxide, dissolving on heating to give a yellow-orange solution, and did not give an insoluble picrate or hydrochloride in benzene. (VI) itself was not acetylated smoothly, though when an equivalent quantity of triethylamine was present, the above acetyl derivative was obtained. With only a trace of triethylamine, however, an acetyl derivative, m. p. 137°, was secured, which appeared to be the same as that obtained from (I) and acetic anhydride–triethylamine (see below). When (VI) was covered with acetic anhydride and a drop of pyridine added, immediate reaction led to the separation of a colourless crystalline mass, m. p. 95° (vigorous decomp.) (after being washed with ethanol). This was clearly of a different character from the other acetyl derivatives mentioned in this section. (VII) dissolved in hot acetic anhydride–pyridine to give an orange solution; dilution with water and crystallisation of the product from aqueous ethanol then gave colourless needles, m. p. 173° (slight decomp.). When (VII) was boiled for a few moments with acetic anhydride–triethylamine, cooled, and diluted with ethanol, a *triacetyl* derivative was obtained which crystallised from ethanol in rosettes of small needles, m. p. 147° (Found: C, 44·8; H, 3·6; N, 9·9; S, 21·7. $C_{11}H_{10}O_4N_2S_2$ requires C, 44·3; H, 3·4; N, 9·4; S, 21·5%). The compound did not yield a picrate in benzene, and was deacetylated with warm 2*N*-hydrochloric acid to give a product, m. p. 165° (decomp.). 2-Thio-5-thiazolidone (I) was suspended in acetic anhydride; addition of triethylamine caused an exothermic reaction and development of a red colour. After 2 hours, the *triacetyl* derivative was collected and recrystallised from chloroform–ethanol, having m. p. 135—137° (Found: C, 38·6; H, 2·8; N, 8·1; S, 34·3. $C_{11}H_{10}O_4N_2S_4$ requires C, 38·6; H, 2·7; N, 7·5; S, 34·2%). Attempts to recrystallise the material from dilute acetic acid or ethanol led to deacetylation, and the production of a compound, m. p. 198° (decomp.), which was reconverted into the original triacetyl derivative by acetic anhydride–triethylamine. The triacetyl derivative was insoluble in cold 2*N*-sodium hydroxide, but dissolved on warming.

Polymerisation of (I).—2-Thio-5-thiazolidone (1·0 g.) was kept in the dark in pyridine (10 c.c.) for 18 hours under nitrogen, and the yellow solid (0·45 g.) which had separated, was washed well with pyridine and then with acetone (Found, after drying for 4 hours at 100°/0·1 mm.: C, 38·5; H, 5·1; N, 14·4; S, 6·4%). The substance decomposed indefinitely above 200°, and was insoluble in common solvents, including hot pyridine and acetic acid. It was almost wholly soluble in aqueous sodium hydrogen carbonate, carbonate, or hydroxide, but only a small recovery was obtained on acidification of such solutions. It was soluble in concentrated hydrochloric acid and in hot dilute acid, though almost insoluble in hot water. In another experiment, (I) (0·2 g.) was boiled with pyridine (5 c.c.) for 2—3 minutes under nitrogen, and the polymer filtered off, washed well with pyridine, and dried for 4 hours at 100°/0·1 mm. [Found: C, 38·4; H, 5·5; N, 19·5; S, 5·5; amino-N (Van Slyke; kindly determined by Dr. J. L. Bailey), 2·3%].

2-Thio-5-thiazolidone (0·5 g.) was heated under reflux with methanol (10 c.c.) for a few minutes in nitrogen, and the colourless granular product filtered off and well washed with hot methanol (Found (in 2 different samples, both dried for 3 hours at 80°/0·1 mm.): C, 37·7, 38·7; H, 5·4, 5·5; N, 19·7, 20·0; S, 7·75, 7·6; MeO, 5·8. $C_{12}H_{18}O_4N_4S_4$ (*i.e.*, $HS_2C{\cdot}[NH{\cdot}CH_2{\cdot}CO]_2{\cdot}OMe$) requires C, 38·4; H, 5·0; N, 19·9; S, 11·3; MeO, 5·7%). Similar results were obtained by using ethanol, though

precipitation was slower. The products were soluble in concentrated hydrochloric acid, and in sodium hydroxide on warming, but could not be suitably recovered by dilution with water or acidification, respectively. They were insoluble in hot pyridine or acetic acid, but readily soluble in formic acid.

We express our gratitude to Sir Ian Heilbron, D.S.O., F.R.S., for his interest, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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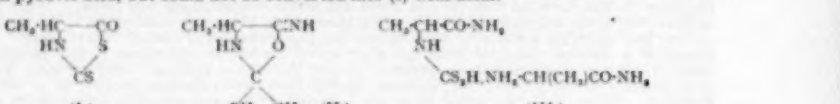
124. *Studies in the Azole Series. Part XXVI. The Action of Bases on 2-Thio-4-methyl-5-thiazolidone.*

By A. H. COOK and A. L. LEVY.

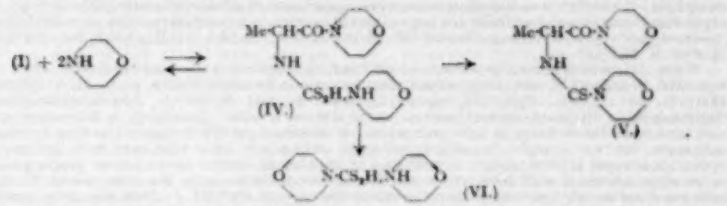
2-Thio-4-methyl-5-thiazolidone (I) exhibits a markedly greater stability than its analogue discussed in the preceding paper. While the ring is still readily opened by ammonia and morpholine, the products tend to revert in large part to (I) on acidification, even under anhydrous conditions. The carbon disulphide can be liberated from the ammonium dithiocarbamate, however, by very slow acidification in water under controlled conditions. (I) polymerises in boiling pyridine, but is stable to cold triethylamine.

IN view of the reactivity of 2-thio-5-thiazolidone and as a model for 4-substituted thiothiazolidones, (±)-2-thio-4-methyl-5-thiazolidone (I) was selected for study. The preparation of α-aminopropionitrile was improved, and the base condensed with acetone in the presence of sodium methoxide (cf. Cook, Heilbron, and Levy, Part III, *J.*, 1948, 201) to give 5-imino-2 : 2 : 4-trimethyloxazolidine (II). With carbon disulphide in wet acetone, this afforded *α-carbamylethylammonium α-carbamylethyldithiocarbamate* (III), which yielded the required *thiothiazolidone* (I) in 90% yield on acidification with two equivalents of 2*N*-sulphuric acid. Acidification with dry hydrogen chloride in ethanol gave alanine amide hydrochloride in 60% yield, also obtained from (II) and hydrochloric acid. While α-aminopropionitrile was available, advantage was taken of the experience gained with aminoacetonitrile, to improve its condensation with carbon disulphide (Cook, Heilbron, and Levy, *J.*, 1947, 1598), and *4-amino-2-mercapto-4-methylthiazole* was obtained directly in 61% yield. It readily formed a Schiff's *base* with pyruvic acid, but could not be converted into (I) with acids.



When (I) was treated with ammonia in ethanol, 90% of *ammonium α-carbamylethyldithiocarbamate* (cf. III) rapidly crystallised. On acidifying a solution of the ammonium salt in water, (I) was recovered in high yield, but treatment with dry hydrogen chloride in ethanol gave crude alanine amide hydrochloride in 64% yield, only 12% undergoing ring-closure to (I). Alternatively, methanolic picric acid could be used to provide crude alanine amide picrate in 70% yield, ammonium picrate being recovered quantitatively. It was of interest to see, using ammonium α-carbamylethyldithiocarbamate as a model, whether carbon disulphide could also be detached by a more controlled acidification in water. It was therefore slowly titrated against 0·05*N*-hydrochloric acid, the changes in pH being followed with a glass electrode. The initial pH (6·26) fell on addition of acid as the dithiocarbamic acid corresponding to (III) was liberated. Thereafter the pH began to rise, following a unimolecular curve and becoming constant after about five minutes. Clearly, this stage corresponded to loss of carbon disulphide from α-carbamylethyldithiocarbamic acid to give alanine amide, which would however be expected to neutralise at once any undecomposed acid to give (III), resulting in only half the theoretical quantity of carbon disulphide being lost for each addition of acid. This was borne out by the final titration curve which showed that two equivalents of acid were required to expel all the carbon disulphide. The course was constructed by observing the pH of the solution at an arbitrarily standardised time of three minutes after the addition of each drop of acid, *i.e.*, when about 85% of the α-carbamylethyldithiocarbamic acid had decomposed. Carbon disulphide separated from the solution during the titration, which took several hours, and no thiothiazolidone (I) was produced. For comparison, ammonium α-carbamylethyldithiocarbamate was titrated

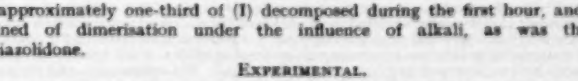
against 0·1N-hydrochloric acid during 11 minutes; in this case (I) separated from the solution, and the curve obtained was quite different from that obtained by slow titration, the first half being of the expected form for neutralisation of an ammonium salt. It appeared, therefore, that very slow acidification allowed α-carbamylethyldithiocarbamic acid to decompose before the pH became sufficiently low to cause thiothiazolidone formation. In order to gain some estimate of this pH value, the ammonium salt was acidified with a series of buffer solutions (pH 1·26—2·8). Crystallisation of (I) practically ceased at pH 2·5, though by working with a very concentrated solution a small degree of cyclisation was brought about by potassium hydrogen phthalate (pH 4). Hence, ring-closure of (III) and the corresponding ammonium salt to (I) was readily effected by such compounds as aqueous oxalic, sulphurous, and acetic acids, an 85% yield being obtained with acetic acid.



When (I) was kept with two equivalent proportions of morpholine in acetone solution, the crystalline *morpholinium* salt of *N*-dithiocarboxyalanine morpholide (IV) soon separated in a yield of 89%. Acidification of this salt regenerated (I) in a yield of 87%. The salt was remarkably labile, for when kept for a short time in solvents it was completely decomposed to a mixture of the substituted *thiourea* (V) and the morpholinium salt of 4-dithiocarboxymorpholine (VI), each of which could be isolated under appropriate conditions. When (I) was warmed with excess of morpholine, (VI) was the main product, treatment of which with aqueous acid gave the corresponding unstable free dithiocarbamic acid. Acidification of (IV) with dry hydrogen chloride in chloroform gave a poor yield of crude alanine morpholide hydrochloride, and 44% of the dithiocarbamate reverted to (I). This contrasts with the ready expulsion of carbon disulphide from the corresponding glycine derivative (preceding paper), and indicates the considerable influence of the methyl substituent in promoting ring-closure.

Again unlike 2-thio-5-thiazolidone, (I) was unaffected by triethylamine in cold acetone, and did not yield an insolubie polymer when heated under reflux with methanol However, in boiling pyridine, a high-melting, insoluble compound was produced after some time, which is probably a lower polyalanine.

The thiothiazolidone (I) dissolved in one equivalent of aqueous barium hydroxide or potassium hydroxide to give a solution of pH 8·5, which slowly became more acid on storage. When the pH had reached 7·7 (after 11 minutes) colourless needles began to separate, which increased in amount during several hours. Surprisingly, these were identified as (I), and its formation was evidently due to slow ring-opening of (VII) to give the carboxylic acid (VIII), which being a comparatively strong acid captured the limited number of potassium ions present from the weakest acid, namely (I). The salt (VII) was also decomposed by carbon dioxide to give (I).



At pH 9, approximately one-third of (I) decomposed during the first hour, and no evidence was obtained of dimerisation under the influence of alkali, as was the case with 2-thio-5-thiazolidone.

Experimental.

2-Thio-4-methyl-5-thiazolidone and Related Compounds.—In our hands, the following preparation of α-aminopropionitrile gave better results than that described in Part II (*J.*, 1947, 1598), and by Goldberg and Kelly (*J.*, 1947, 1371). Acetaldehyde (180 g.; freshly prepared from paraldehyde) and hydrogen cyanide (160 c.c.) were mixed in a large flask cooled in a freezing mixture, 50% aqueous potassium hydroxide cautiously added to initiate the vigorous autocatalytic reaction, and addition subsequently continued until no further heating effect was produced (2—3 c.c. required). After 1 hour

at room temperature, the catalyst was neutralised with concentrated sulphuric acid, and the mixture filtered and distilled at 10—12 mm. After an initial fraction, b. p. ~50° (paraldehyde), acetaldehyde cyanohydrin (105 g., 36%) distilled smoothly at 92°. Commercial acetaldehyde gave variable results by this procedure, though one batch (600 g.) gave a 60% yield of cyanohydrin. The cyanohydrin (107 g.) was added to a solution of liquid ammonia (100 g.) in methanol (500 c.c.), and the mixture kept at room temperature for 22·5 hours. Excess of methanol and ammonia was removed in a vacuum, and the residue distilled at 10—12 mm., an initial fraction (mainly water) being followed by the pure α-aminopropionitrile (78·5 g., 48%), b. p. 64°.

α-Aminopropionitrile (10 g.) in dry acetone (20 c.c.) was treated with a solution of sodium (~0·2 g.) in dry ethanol (~2 c.c.), the mixture becoming slightly warm. Next morning, the mixture was cooled in a freezing mixture and scratched, whereupon 5-imino-2 : 2 : 4-trimethyloxazolidine (9·2 g., 50%) separated, having m. p. 76°. Like the glycine analogue, it was deliquescent, but solidified again owing to carbonate or carbamate formation. With concentrated hydrochloric in ethanol, it yielded alanine amide hydrochloride, m. p. 172—173°. When the above acetone filtrate was treated with carbon disulphide, it yielded *α-carbamylethylammonium α-carbamylethyldithiocarbamate* (III) (4·0 g.), which crystallised from water on addition of a large excess of acetone, in rectangular tablets, m. p. 140° (decomp.) (varies with the rate of heating) (Found: C, 33·35; H, 6·6; N, 22·5. $C_7H_{14}O_2N_4S_4$ requires C, 33·35; H, 6·4; N, 22·2%).

When (III) was dissolved in water, and acidified, the required *2-thio-4-methyl-5-thiazolidone* rapidly separated in high yield, and recrystallised from benzene in beautiful blades, m. p. 128·5° (Found: C, 33·0; H, 3·8; N, 9·3. $C_4H_5ONS_2$ requires C, 32·65; H, 3·4; N, 9·5%). The thiothiazolidone was freely soluble in methanol, ethanol, acetone, ethyl acetate, or ether, moderately in chloroform or acetic acid, and insoluble in water or light petroleum. It dissolved readily in aqueous sodium hydroxide or carbonate, but was insoluble in sodium hydrogen carbonate. After treatment with hydroxylamine hydrochloride and sodium acetate in methanol, it afforded an intense brown colour (and a precipitate in stronger solutions) with ferric chloride. 2-Thio-5-thiazolidone gave the same colour (though the iodine–sodium acetate test is more characteristic in this case; cf. Part III, *J.*, 1948, 204), as do many other 4-substituted-5-thiazolidones and anhydrides generally (Davis and Levy, *J.*, in the press).

For the preparation of 2-thio-4-methyl-5-thiazolidone (I) in the best yield, it was not necessary to isolate α-aminopropionitrile or the above iminotrimethyloxazolidine, and a typical procedure was as follows. Acetaldehyde cyanohydrin (80 g.) was added to a mixture of liquid ammonia (40 c.c.) and methanol (40 c.c.) cooled initially in ice, and kept for 24 hours at room temperature. Excess of methanol and ammonia was then evaporated off on a water pump, until the temperature of the distilling liquid had reached 55°, and the residue was dissolved in dry acetone (150 c.c.), treated with sodium ethoxide (~0·5 g.), and kept overnight. The mixture was then diluted with acetone (250 c.c.) containing water (20 c.c.) and seeded, whereafter addition of carbon disulphide (40 c.c.) with vigorous stirring and scratching caused the dithiocarbamate (III) (47·5 g., 33% calc. on the cyanohydrin) to separate. This was dissolved in water and acidified with 2*N*-sulphuric acid (190 c.c.). 2-Thio-4-methyl-5-thiazolidone (25 g., 90%), m. p. 125—126°, rapidly crystallised. Recrystallisation from benzene gave 18 g., m. p. 127—128°.

The dithiocarbamate (III) (1·26 g.) was suspended in dry ethanol (10 c.c.), and a stream of dry hydrogen chloride in nitrogen (made by bubbling nitrogen through concentrated hydrochloric acid, followed by passage through anhydrous calcium chloride) passed in for 2 hours. (III) dissolved, and was replaced by crude alanine amide hydrochloride (0·74 g., 60%), m. p. 165—168°.

α-Aminopropionitrile (4·5 g.) was treated with excess of carbon disulphide in ethyl acetate, whereupon *5-amino-2-mercapto-4-methylthiazole* (5·7 g., 61%) separated on scratching, and recrystallised from ethanol in pale yellow needles which contracted and resolidified at about 150°, became dark purple at 220°, and decomposed completely at 233° (Found: C, 33·4; H, 4·0. $C_4H_6N_2S_2$ requires C, 32·9; H, 4·1%). When the reaction was carried out in ethanol, the product was incompletely soluble in hot ethanol, the residue being 2 : 4-dithio-5-methylhydantoin, m. p. 223° (decomp.) (cf. Cook, Heilbron, and Levy, *loc. cit.*). When the aminothiazole was dissolved in 2*N*-hydrochloric acid, it was rapidly replaced by white needles of the hydrochloride, m. p. 207° (decomp.); on the mixture being warmed to 70° for 1 minute a flocculent precipitate, m. p. 195—200° (decomp.), was deposited. The aminothiazole gave a clear solution in 2*N*-nitric acid, which slowly deposited the above compound, m. p. 195—200° (decomp.), in poor yield on storage for some hours; (I) was not obtained. When treated with pyruvic acid in methanol, the thiazole gave an immediate orange precipitate of *5-α-carboxyethylidenamino-2-mercapto-4-methylthiazole* which crystallised from acetic acid in clusters of needles, m. p. 199° (decomp.) (Found: C, 39·2; H, 3·8. $C_7H_8O_2N_2S_2$ requires C, 38·9; H, 3·7%).

Experiments with Ammonium α-Carbamylethyldithiocarbamate.—2-Thio-4-methyl-5-thiazolidone (2·0 g.) in ethanol (25 c.c.) was treated with liquid ammonia (3 c.c.). Ammonium α-carbamylethyldithiocarbamate (2·2 g., 90%) was collected after 45 minutes, and recrystallised from methanol–ether; it then had m. p. 143°. With aqueous silver nitrate it gave a momentary white precipitate which rapidly became yellow and then black. Lead acetate gave a yellow precipitate which began to deposit a lead sulphide " mirror " after 5 minutes, whereas mercuric chloride gave a clean, almost white derivative.

The ammonium salt (1·0 g.) was suspended in dry ethanol (10 c.c.), and dry hydrogen chloride passed in with cooling until the mixture was acid to Congo-red. Ammonium chloride (0·3 g.) was filtered off, and the filtrate evaporated to dryness in a vacuum and treated with a small volume of ethanol to give crude alanine amide hydrochloride (0·25 g.), m. p. 158° (decomp.). Re-evaporation and trituration of the residue with acetone gave a second crop (0·19 g.), m. p. 154° (decomp.). The final filtrate was evaporated, and the residue treated with water to give (I) (0·08 g., 12%), m. p. 126—128°. The combined crops of amide hydrochloride (0·44 g., 64%) were recrystallised thrice from acetic acid; the colourless needles produced had m. p. 176°, undepressed with an authentic specimen.

Picric acid (1·15 g.) was dissolved in warm methanol (10 c.c.), and a suspension of the above ammonium salt (0·45 g.) in warm methanol (7 c.c.) added. The solution became clear, whereafter cooling in a freezing mixture gave ammonium picrate (0·53 g., 87%), m. p. ~230° (decomp.). The filtrate was evaporated in a

vacuum, and four crops of crude alanine amide picrate (total : 0·58 g., 74%) were obtained by dissolution of the residue in acetone and precipitation with ether and light petroleum. The combined material was recrystallised from water; a small first crop was ammonium picrate, the remainder (0·27 g.; 36%) being alanine amide picrate, m. p. 192—200°, undepressed on admixture with an authentic sample (m. p. 197°).

The slow-titration experiment was performed at 22° on 3·997 mg. (0·0221 mg.-equivalent) of the ammonium salt in water (1·0 c.c.), in a micro-titration apparatus described by Catch, Cook, and Kitchener (*J.*, 1945, 319), using a standard Cambridge pH meter and glass electrode. Addition of 0·897 c.c. of 0·0497N-hydrochloric acid (*i.e.*, 0·0445 mg.-equivalent) was required to reach the end-point. In the rapid-titration experiment, 1·0 c.c. of 0·5N-ammonium α-carbamylethyldithiocarbamate was neutralised with 5·0 c.c. of 0·1N-hydrochloric acid in a Morton cell, stirring being effected with a fine stream of nitrogen.

Buffer solutions of pH 1·26, 1·88, 2·16, 2·5, and 2·8 were prepared by mixing 0·1N-glycine solution (0·1N. also with respect to sodium chloride) with 0·1N-hydrochloric acid in the following proportions : 2 : 8, 5 : 5, 6 : 4, 7 : 3, 8 : 2. 0·5M-Ammonium α-carbamylethyldithiocarbamate (1 c.c.) was added to each (10 c.c.); precipitation of (I) by the first two appeared to be as complete as with 0·05N-hydrochloric acid. A smaller quantity crystallised from the solution having pH 2·16, and hardly any from that having pH 2·5. α-Carbamylethylammonium α-carbamylethyldithiocarbamate (III) (5·0 g.) was dissolved in water and acidified with glacial acetic acid (*ca.* 3 c.c.), whereupon 2-thio-4-methyl-5-thiazolidone (2·45 g., 85%) separated slowly in well-formed plates. When the corresponding ammonium salt was acidified with aqueous picric acid, however, ammonium picrate was precipitated, and (I) was not produced.

Action of Morpholine on (I).—2-Thio-4-methyl-5-thiazolidone (1·5 g.) in acetone (25 c.c.) was treated with morpholine (1·8 g., 2 equivs.). Heat was evolved and the *morpholinium* salt (IV) (2·9 g., 89%) of *N*-dithiocarboxyalanine morpholide separated on scratching, and was recrystallised from chloroform by the addition of ethyl acetate containing a little ether, forming microprisms, m. p. 115° (decomp.; partly resolidifying to remelt at ~175°) (Found : C, 44·2; H, 7·3. $C_{12}H_{22}O_3N_2S_2$ requires C, 44·9; H, 7·2%). The reaction could also be carried out in methanol, the dithiocarbamate separating in well-formed rectangular prisms, m. p. 110° (decomp.), on seeding. If the solution was not seeded, however, the thiourea (V) (see below), m. p. 159°, crystallised on storage overnight, whereas, if the dithiocarbamate (IV) was dissolved in methanol, morpholinium dithiocarbamate (VI) (see below), m. p. 219° (sealed tube), separated on storage (especially if the solution had been warmed).

When the compound (IV) (2·9 g.) was dissolved in water (20 c.c.) and acidified with concentrated hydrochloric acid, 2-thio-4-methyl-5-thiazolidone (1·15 g., 87%), m. p. 123—125°, was immediately precipitated. (IV) (1·0 g.) in dry chloroform (20 c.c.) was saturated with dry hydrogen chloride, and evaporated to dryness in a vacuum. Treatment of the residue with ethanol and then acetone gave 3 crops of crystals (0·68 g., total), the final filtrate giving (I) (0·2 g., 44%), m. p. 124°, on dilution with water. Fractionation of the above crystals from ethanol cooled in a freezing mixture gave the less soluble morpholine hydrochloride, m. p. 175—176°, and crude alanine morpholide hydrochloride, m. p. 153—156°. The latter became damp on exposure to air, changing to a compound, m. p. 251° (decomp.), after crystallisation from ethanol.

In an attempted crystallisation of (IV) from methanol–ethyl acetate, very little of the required compound was obtained, and evaporation of the filtrate yielded the substituted *thiourea* (V), m. p. 159°, which recrystallised from benzene–light petroleum in clusters of rods, m. p. 161—162° (Found : C, 50·0; H, 7·7; N, 14·5. $C_{12}H_{21}O_3N_2S$ requires C, 50·2; H, 7·3; N, 14·6%). It could also be crystallised from water, or in diamond-shaped prisms from methanol or ethanol. When (I) was warmed with excess of morpholine for a few moments without a solvent, morpholinium dithiocarbamate (VI) separated; it recrystallised from water in rhombic tablets which sublimed unchanged at ~200° and melted (sealed tube) at 227° (Found : C, 43·4; H, 7·45; N, 11·1. Calc. for $C_5H_{11}O_3N_2S_2$: C, 43·2; H, 7·2; N, 11·2%). It was best prepared by the action of carbon disulphide on morpholine in acetone, in which it was highly insoluble. This, incidentally, provides a convenient method for the detection of carbon disulphide in small amounts in vapours, etc. When (VI) was dissolved in water and acidified, a white curdy precipitate was produced, which redissolved during one minute.

Action of Tertiary Amines and Aqueous Alkali on (I).—2-Thio-4-methyl-5-thiazolidone (0·73 g.) was kept with triethylamine (0·5 g., 1 equiv.) in acetone (10 c.c.) for 1 hour, and the clear yellow solution acidified with dry hydrogen chloride. Triethylamine hydrochloride was filtered off, and a further crop removed by evaporation and treatment with ether. The filtrate was evaporated, and the residue (0·45 g.), m. p. 116°, washed with water. Crystallisation from benzene gave (I), m. p. 125°, and a small insoluble residue, m. p. 210° (decomp.), soluble in aqueous sodium hydroxide and reprecipitated on acidification.

The thiazolidone (I) (1·0 g.) was heated under reflux with pyridine (10 c.c.) for 30 minutes, and the resulting gel diluted with methanol to granulate the *polymer*, which contracted considerably when dried at 100° (Found : C, 47·2; H, 7·2; N, 17·4; S, 0·38%). It was a white powder, m. p. ~290°, insoluble in common solvents. (I) (1·0 g.) was destroyed when heated under reflux with methanol (10 c.c.) for 1 hour; the product was oily and readily soluble in organic liquids.

Saturated solutions of (I) in 0·34N-barium hydroxide and 0·5N-potassium hydroxide deposited colourless needles, m. p. 126°, of (I) after a short while (see p. 643). An attempt was made to follow the decomposition of (I) with alkali, by keeping the pH constant at 9 with small progressive additions of 0·34N-barium hydroxide. The readings became variable and unreliable after about 30 minutes, but it was established that about 33% of (I) decomposed during the first hour.

We are grateful to Sir Ian Heilbron, D.S.O., F.R.S., for his interest and encouragement, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

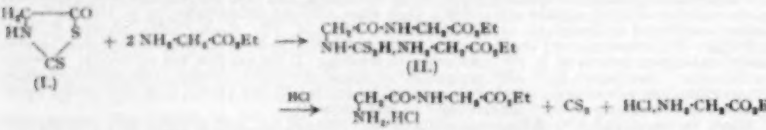
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7. [*Received, November 15th*, 1949.]

125. *Studies in the Azole Series. Part XXVII. A New Method of Peptide Synthesis: Glycyl Peptides.*

By A. H. Cook and A. L. Levy.

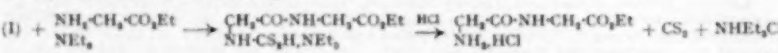
2-Thio-5-thiazolidone (I) is a useful reagent for the addition of a glycyl residue to the ester of an α-amino-acid or peptide in a single operation. Coupling takes place in the presence of a tertiary base and the product is released by acidification. In this way, for example, the polyglycine esters up to pentaglycine ethyl ester hydrochloride (III) have been prepared stepwise from glycine ester, in good yields at each stage. α-Amino-acid or peptide esters are very suitable for partition chromatography on paper, and may be revealed by the use of ninhydrin in the usual way.

In Part XIX (Billimoria and Cook, *J.*, 1949, 2323) anhydrocarboxyglycine was shown to be too reactive to allow a useful synthesis of glycylglycine ester. In Part XXV, however (*J.*, 1950, 637) a method for the controlled preparation of glycine amides from the dithio-analogue, 2-thio-5-thiazolidone (I), was established in principle, using morpholine as a model base. In the present paper, the application of this reaction to α-amino-esters is described and shown to provide a ready method for the synthesis of glycyl peptides.

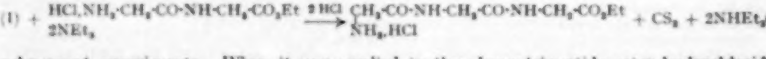


When 2-thio-5-thiazolidone (I) was treated with two equivalents of glycine ethyl ester in ethyl acetate, the dithiocarbamate (II) separated as an uncrystallisable oil. In chloroform, however, a clear solution resulted and, when this was treated directly with dry hydrogen chloride and evaporated, a mixture of glycine ester hydrochloride and glycylglycine ester hydrochloride was obtained. A better procedure was to conduct the initial condensation in ethanol, acidification of the clear solution with ethanolic hydrogen chloride causing separation of the crude peptide ester hydrochloride in 78% yield. This was freed from glycine ester hydrochloride by one crystallisation from ethanol, the yield of pure material being then 50%.

Glycylglycine ethyl ester (two equivalents) was added to one equivalent of (I) in ethanol, followed almost immediately by two equivalents of ethanolic hydrogen chloride, which caused rapid separation of almost pure triglycine ester hydrochloride in 96% yield, the filtrate yielding crystals of the dipeptide ester hydrochloride on storage. Treatment of (I) with one equivalent only of glycine ester gave a poor yield of impure dipeptide. However, (I) reacted smoothly with a mixture of one equivalent each of glycine ester and triethylamine in chloroform, and acidification then caused pure glycylglycine ester hydrochloride to separate in 57% yield, triethylamine hydrochloride being soluble in chloroform.



The peptide ester hydrochlorides may conveniently be converted into the bases *in situ* by treating the thiothiazolidone directly with an amino-ester hydrochloride and two equivalents of triethylamine. Thus, (I) in ethanol gave an 86% yield of the tripeptide ester hydrochloride, the yield of glycylglycine ester by this procedure being 70%. This general method was used in



subsequent experiments. When it was applied to the above tripeptide ester hydrochloride, tetraglycine ethyl ester hydrochloride was obtained in a yield of 88%. The latter gave a strong biuret reaction, unlike the starting material and lower peptides. This fact is responsible for the trivial name " biuret base " given by Curtius (*Ber.*, 1883, **16**, 755; 1904, **37**, 1286) to the tetrapeptide ester, which he prepared by keeping glycine ester for several weeks in anhydrous ether. Curtius recorded for the hydrochloride m. p. 192—193°, whereas Fischer (*Ber.*, 1904, **37**, 2504), who prepared the compound by esterification of tetraglycine, gave a value of 212—214°. We have confirmed the latter figure and shown by paper chromatography that the material prepared

by tetramerising glycine ester contains a small proportion of penta- and hexa-peptides which depress the melting point.

$$HCl,NH_2\cdot[CH_2\cdot CO\cdot NH]_4\cdot CH_2\cdot CO_2Et \quad \text{(III.)}$$

Conversion of " biuret base " hydrochloride into the *pentapeptide ethyl ester hydrochloride* (III) in a yield of 85% was achieved in a similar fashion, except that 92% methanol was required to dissolve the more complex starting material. It has previously been demonstrated with the model tripeptide synthesis, that the method was still applicable in the presence of 75% ethanol, though the yield dropped to 64% as compared with 86% in the anhydrous solvent, a result which was not unexpected in view of the known fission of *N*-dithiocarboxyglycine amides by aqueous acids.

The general procedure was applicable also to amino-esters other than glycine, in both their optically active and their racemic forms. Thus when L-tyrosine methyl ester was treated with (I) and triethylamine in chloroform, addition of dry hydrogen chloride gave *glycyl-L-tyrosine methyl ester hydrochloride* in a yield of 50%. This yield dropped to 20% when two equivalents of triethylamine were present, but increased slightly to 37% with 1·5 equivalents each of (I) and triethylamine. Similarly, DL-phenylalanine ester gave glycyl-DL-phenylalanine methyl ester hydrochloride in a yield of 30% which was not improved by several variations in the reaction conditions. When 2-thio-4-phenyl-5-thiazolidone (Billimoria and Cook, *loc. cit.*) became available, it was condensed with glycylglycine ester hydrochloride, giving 37% of *α-phenyl-*

$CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO\cdot NH_2$	$CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO\cdot NH_2$	$CH_2\cdot CO\cdot NH\cdot CH(CH_2Ph)\cdot CO_2H$
$NH\cdot CS_2H,NH_2\cdot CH_2\cdot CO\cdot NH_2$	$NH\cdot CS\cdot S\cdot CH_2Ph$	$NH\cdot CS_2H$
(IV.)	(V.)	(VI.)

glycylglycine ethyl ester hydrochloride. The reality of the dithiocarbamate intermediates postulated above was shown by the isolation of (IV), characterised as the *benzyl* ester (V), after reaction of (I) with glycine amide in ethanol.

Unlike most free peptides, the peptide ester hydrochlorides which resulted from the synthesis were highly crystalline substances with sharp melting or decomposition points, which were depressed strongly by the presence of impurities. In many cases they proved more suitable than the free peptides for analysis by partition chromatography on paper (for a review, see Consden, *Nature*, 1948, **162**, 359) because their higher R_F values led to much more satisfactory separation. This was well exemplified by the above polyglycine ester hydrochlorides and the corresponding free peptides obtained by hydrolysis. With the salts the paper chromatograms, with butanol–acetic acid as the mobile phase, showed a regular decrease in the R_F value by a factor of about ½ for each additional glycine residue, except the first. A similar relation holds in the other polyglycine series mentioned below. By paper chromatography, it was shown that glycine was produced when (I) was warmed to 70° in water, whereas in more concentrated solution loss of carbon disulphide was accompanied also by the formation of lower polyglycines and the presence of those up to pentaglycine was demonstrated. In a similar fashion, the lower five polyglycyl-peptides of L-tyrosine, methionine, norvaline, phenylalanine, and isoleucine were produced by heating (I) with the appropriate amino-acid in water, or better, glacial acetic acid, and readily identified by paper chromatography. The R_F values of a number of amino-acids, glycyl-peptides, and their esters in butanol–acetic acid are collected at the end of the Experimental section.

In the case of alanine, methionine, and valine methyl esters, reaction with (I) under the standard conditions mentioned above failed to yield crystalline dipeptide ester hydrochlorides, though their formation was clearly shown by paper chromatography. This analysis also indicated the formation of several other ninhydrin-reactive substances in small amounts from such syntheses; glycine methyl ester hydrochloride and the dimeride of (I) (Part XXV, *loc. cit.*) were identified. The former was produced by reaction of (I) with the methanol used as solvent in that case, and the latter by the action of triethylamine, though the emergence of peptides in substantial yield from such reactions shows that dimerisation is slow compared with the ring-opening of (I) by amines. In such cases where the esters were not readily crystallised, the method could still be used to provide the desired peptide by hydrolysis of the crude ester and chromatography of the product on a column of cation-exchange resin (see the succeeding paper). This was illustrated by the case of glycylvaline, which was thus obtained crystalline.

Finally, it has been shown that (I) can also be utilised preparatively to give a glycyl-peptide by reaction with a free amino-acid. Thus, rapid fission occurred when (I) was shaken with a

solution of phenylalanine in two equivalents of sodium hydroxide, and on acidification a heavy yellow oil was produced which was probably the dithiocarbamic acid (VI). When this was dissolved in acetone, glycyl-DL-phenylalanine rapidly crystallised in 25% overall yield. The isolation of (VI) appeared to result from the hydrophobic character of the phenylalanine residue.

While the classical methods of peptide synthesis are too well known to require additional mention here, the use of anhydro-*N*-carboxyamino-acids bears a close relation to the present method and deserves therefore to be briefly reviewed. The first such compound, anhydro-*N*-carboxyglycine, was prepared by Leuchs (*Ber.*, 1906, **39**, 857), and some 20 additional members of the series have since been made. Interest has centred mainly on their ability to polymerise to polypeptides of high molecular weight with loss of carbon dioxide (cf., *inter alia*, Astbury, Dalgliesh, Darmon, and Sutherland, *Nature*, 1948, **162**, 596), but the formation of monomeric amides and peptides has been noted on several occasions. Thus anhydro-*N*-carboxy-*N*-phenylglycine was converted into the amide (Leuchs and Manasse, *Ber.*, 1907, **40**, 3235), anilide (Fuchs, *Ber.*, 1922, **55**, 2943), ethylamide, methylanilide, and piperidide of *N*-phenylglycine (Wessely, *Z. physiol. Chem.*, 1925, **146**, 72) and the corresponding peptides with glycine, glycine ester, and tyrosine ester (*idem*, *ibid.*). Anhydro-*N*-carboxy-β-phenylalanine gave the anilide (Curtius and Sieber, *Ber.*, 1922, **55**, 1543), amide, ethylamide, and 2 : 2-diethoxyethylamide of phenylalanine (Wessely and Sigmund, *Z. physiol. Chem.*, 1926, **157**, 91), and with glycine and glycylglycine gave the peptides phenylalanylglycine and phenylalanylglycylglycine; with tyrosine ester the peptide ester cyclised to phenylalanyltyrosine anhydride, and with aniline, phenylalanylphenylalanylanilide was isolated (*idem*, *ibid.*). By reaction of anhydro-*N*-carboxy-β-phenylalanine with aniline and methylaniline picrates, the corresponding phenylalanine amide picrates were obtained, and the same technique was also used successfully for anhydro-*N*-carboxyglycine (Wessely and John, *Monatsh.*, 1927, **48**, 11). The latter anhydride has recently been condensed with morpholine and glycine ester at a low temperature (Billimoria and Cook, *loc. cit.*). Reaction of D-anhydro-*N*-carboxyalanine with 2 equivalents of L-histidine ester in chloroform has yielded D-alanyl-L-histidine (31%), after hydrolysis (Hunt and Du Vigneaud, *J. Biol. Chem.*, 1938, **125**, 699).

In these simple cases, polymerisation is minimised by the effect of three factors, separately or in combination: (1) The loss of carbon dioxide is slow compared with the initial ring-opening reaction; this is ensured either by the effect of substituents in the oxazolid-dione ring (*e.g.*, with the derivatives of alanine and phenylalanine; cf. also 2-thio-5-thiazolidones) or by cooling (*e.g.*, with anhydrocarboxyglycine). (2) The initiating amine is usually a stronger base than that produced by loss of carbon dioxide (*e.g.*, with anhydro-*N*-carboxy-*N*-phenylglycine). (3) Where the initiating amine is a weaker base than that produced by loss of carbon dioxide, the latter is preferentially engaged by an acid, *e.g.*, picric acid, included in the medium. The use of 2-thio-5-thiazolidones described in the present paper entails the use of stable crystalline compounds which give rise to little or no complications of polymerisation.

Experimental.

Reaction of (I) *with Glycine Ethyl Ester.*—(*a*) 2-Thio-5-thiazolidone (0·68 g.) was suspended in chloroform (15 c.c.). Addition of glycine ethyl ester (1·0 g., 2 equivs.) caused dissolution with evolution of heat. Dry hydrogen chloride was passed in, the solution evaporated, and the residue treated with ethanol, to give crude glycylglycine ester hydrochloride, which had m. p. 185—186° after a further crystallisation from ethanol.

(*b*) 2-Thio-5-thiazolidone (0·66 g.) in ethanol (10 c.c.) was treated with glycine ethyl ester (1·0 g., 2 equivs.), followed after 10 minutes by 10*N*-ethanolic hydrogen chloride (1 c.c., 2 equivs.). Glycylglycine ethyl ester hydrochloride (0·77 g.), m. p. 155—170°, separated on cooling in ice, and was recrystallised from ethanol to give the pure compound (0·5 g.), m. p. 183—184°.

Reaction of (I) *with Glycylglycine Ethyl Ester.*—Glycylglycine ethyl ester hydrochloride (Fischer and Fourneau, *Ber.*, 1901, **34**, 2868) (8·0 g.) was suspended in chloroform and shaken rapidly with potassium hydroxide (2·5 g.) in water (3 c.c.). The chloroform was twice replaced, and the combined extracts dried (Na_2SO_4) and evaporated, to yield the free base (4·5 g.), m. p. 87—88°. The base (1·6 g., 2 equivs.) in ethanol (10 c.c.) was added to 2-thio-5-thiazolidone (0·66 g.) in ethanol (15 c.c.), and the solution acidified with 10*N*-ethanolic hydrogen chloride (1 c.c., 2 equivs.) after 10 minutes at room temperature. The mixture set to a solid mass of triglycine ethyl ester hydrochloride (1·2 g., 96%), m. p. 213° (decomp.) (lit., m. p. 214°), and overnight the filtrate deposited crystals of the dipeptide ester hydrochloride (0·3 g.), m. p. 180—181°, a further crop being obtained by addition of ether.

Reaction of (I) *with Glycine Ester and Triethylamine.*—2-Thio-5-thiazolidone (0·66 g.) was suspended in chloroform (10 c.c.) and cooled to 0°. A mixture of glycine ethyl ester (0·51 g., 1 equiv.) and triethylamine (0·5 g., 1 equiv.) in chloroform (2 c.c.) was added during 15 minutes, and the solution kept for a further 15 minutes in the ice bath. Acidification with 10*N*-ethanolic hydrogen chloride (1 c.c., 2 equivs.) then gave glycylglycine ethyl ester hydrochloride (0·57 g., 57%), m. p. 182—183°, which was collected after 2 hours at 0°. From the filtrate, overnight, a small quantity (0·05 g.) of material, m. p. 208°, was obtained.

Glycylglycine Ethyl Ester Hydrochloride.—A warm suspension of glycine ethyl ester hydrochloride (0·7 g.) in ethanol (5 c.c.) containing triethylamine (1·0 g., 2 equivs.) was added to 2-thio-5-thiazolidone (0·66 g.) in ethanol (5 c.c.), and the mixture acidified with 10*N*-ethanolic hydrogen chloride after 15 minutes. The product (1·17 g.), collected after 1 hour at 0°, was recrystallised from ethanol (containing free hydrogen chloride) to give somewhat impure glycylglycine ethyl ester hydrochloride (0·68 g., 70%), m. p. 162—169°.

Triglycine Ethyl Ester Hydrochloride.—2-Thio-5-thiazolidone (10 g.) was added to a mixture of glycylglycine ethyl ester hydrochloride (15 g., 1 equiv.) and triethylamine (15 g., 2 equivs.) in ethanol (150 c.c.), and the clear solution acidified with 5*N*-ethanolic hydrogen chloride (30 c.c., 2 equivs.). On seeding of the solution, triglycine ethyl ester hydrochloride (16·7 g., 86%) separated as a mass of plates, m. p. 213—214° (decomp.), which, recrystallised from water–acetone, had m. p. 216—217° (decomp.).

(I) (0·66 g., 1 equiv.) in 75% ethanol (10 c.c.) was treated with a solution of glycylglycine ester (0·80 g., 1 equiv.) and triethylamine (0·50 g., 1 equiv.) in 75% ethanol (5 c.c.), and acidified after a few minutes with 10*N*-ethanolic hydrogen chloride. Triglycine ester hydrochloride (0·8 g., 64%), m. p. 217—218° (decomp.), was then caused to separate by addition of ether. In an otherwise similar experiment, acidification was effected with 50% hydrogen bromide in acetic acid, whereupon the beautifully crystalline *triglycine ethyl ester hydrobromide* separated on scratching, and was recrystallised from ethanol, whereupon it had m. p. 191° (Found: C, 32·5; H, 5·5. $C_8H_{16}O_4N_3Br$ requires C, 32·2; H, 5·4%). The compound was soluble in methanol and insoluble in acetone.

Tetraglycine Ethyl Ester Hydrochloride.—Triglycine ethyl ester hydrochloride (12·6 g.) was shaken with triethylamine (10 g., 2 equivs.) in ethanol (400 c.c.) and filtered from a small quantity (0·8 g.) of undissolved ester. 2-Thio-5-thiazolidone (6·6 g., 1 equiv.) was added, and the solution seeded and acidified at once with ethanolic hydrogen chloride (2 equivs.), whereupon tetraglycine ethyl ester hydrochloride (12·3 g.) rapidly separated. A further 0·5 g. (total yield, 88%) of crystalline material was deposited from the filtrate. The main crop contained a small quantity of bound sulphur, which could be removed by dissolution in boiling water, filtration, and crystallisation of the "biuret base" hydrochloride as lustrous platelets, m. p. 213—214° (decomp.) (8·75 g.), by addition of ethanol containing a little free hydrogen chloride.

"Biuret base" hydrochloride prepared according to Curtius (*loc. cit.*) had m. p. 195—199° (decomp.), raised to 199—202° by one crystallisation from aqueous ethanol. With aqueous picric acid it gave a picrate, m. p. 222° (decomp.) (lit., m. p. 189°), not depressed on admixture with the picrate of "biuret base" prepared by the present method. Paper chromatography of the Curtius "biuret base" hydrochloride on Whatman No. 1 paper, with butanol–acetic acid as the mobile phase, gave three spots of R_F 0·19, 0·11, and 0·065, respectively; the first two corresponded to the known tetra- and penta-peptide ester hydrochlorides of glycine, and the third was presumed to be due to the hexapeptide.

When the above pure hydrochloride was dissolved in the minimum volume of water, addition of triethylamine caused precipitation of the free "biuret base," which crystallised well from methanol in clusters of needles or platelets. It dissolved when suspended in methanol, and the solution was treated with hydrogen bromide in acetic acid, whereafter addition of ether caused separation of *tetraglycine ethyl ester hydrobromide*, which recrystallised from ethanol as plates (Found: C, 33·8; H, 5·4. $C_{10}H_{19}O_5N_4Br$ requires C, 33·8; H, 5·4%).

Pentaglycine Ethyl Ester Hydrochloride.—Tetraglycine ethyl ester hydrochloride (5·0 g., 1 equiv.) was dissolved in water (12·5 c.c.) and solutions of triethylamine (3·2 g., 2 equivs.) in methanol (25 c.c.) and finely powdered 2-thio-5-thiazolidone (2·11 g., 1 equiv.) in methanol (65 c.c.) were rapidly added, a clear, pale pink solution resulting. Acidification with 5*N*-ethanolic hydrogen chloride (7 c.c.), seeding, and scratching gave the required pentapeptide ester hydrochloride (4·6 g.), m. p. 227—228° (decomp.), and a further 0·4 g. (total yield, 85%), m. p. 224° (decomp.), separated from the filtrate on storage. *Pentaglycine ethyl ester hydrochloride* recrystallised from aqueous acetone or aqueous methanol containing a little free hydrogen chloride as laths, m. p. 236—237° (decomp.) (Found: C, 39·5; H, 6·0. $C_{12}H_{23}O_6N_6Cl$ requires C, 39·2; H, 6·0%). With aqueous picric acid, it yielded a picrate, m. p. 230—231° (decomp.).

Glycyl-L-tyrosine Methyl Ester Hydrochloride.—L-Tyrosine methyl ester (0·97 g.) was boiled with chloroform (20 c.c.) and then rapidly cooled, triethylamine (0·5 g., 1 equiv.) followed by 2-thio-5-thiazolidone (0·66 g., 1 equiv.) was added, and the whole was shaken. After 4 hours, the purple solution was acidified with 10*N*-ethanolic hydrogen chloride (2 c.c.), and the product (0·7 g., 50%), m. p. 204° (decomp.), which was at first gummy but later crystalline, filtered off and washed with chloroform and then acetone. *Glycyl-L-tyrosine methyl ester hydrochloride* recrystallised best from methanol–ethyl acetate. It had m. p. 223 (decomp.) (Found: C, 49·4; H, 5·7; N, 9·95. $C_{12}H_{17}O_4N_2Cl$ requires C, 49·9; H, 5·9; N, 9·7%).

L-Tyrosine methyl ester (5·0 g.) was boiled with chloroform (150 c.c.) for 10 minutes, and filtered hot. To the warm filtrate was added triethylamine (3·75 g., 1·5 equivs.) and 2-thio-5-thiazolidone (5·0 g., 1·5 equivs.), and the mixture was kept overnight at room temperature. Dry hydrogen chloride was passed in until the solution was saturated, and the sticky gum which had separated rubbed with portions of chloroform to remove triethylamine hydrochloride and crystallised (3·8 g.), m. p. 217° (decomp.), by addition of acetone. The decanted chloroform slowly deposited a further 0·4 g. (total yield, 57%) of product. Recrystallisation from methanol–ethyl acetate gave the pure peptide ester hydrochloride (3·0 g.), m. p. 222—223° (decomp.).

Glycyl-DL-phenylalanine Ethyl Ester Hydrochloride.—DL-Phenylalanine methyl ester hydrochloride 1·08 g.) was dissolved in chloroform (75 c.c.) containing triethylamine (1·0 g., 2 equivs.), and the whole added to a suspension of 2-thio-5-thiazolidone (0·66 g., 1 equiv.) in chloroform (5 c.c.). Reaction appeared slower than usual, and after 30 minutes at room temperature the solution was acidified with 10*N*-ethanolic hydrogen chloride (2 c.c.), seeded, and cooled in ice for 4·5 hours. The glycyl-DL-phenylalanine methyl ester hydrochloride which separated (0·39 g., 30%) was washed with acetone and had m. p. 166°, undepressed on mixing with a sample made by esterifying glycyl-DL-phenylalanine (Leuchs and Suzuki, *Ber.*, 1904, **37**, 3312). The yield was not improved by addition of triethylamine to the other

two components during 1 hour, by the alternative use of pyridine, or by reaction of the thiazolidone with 2 equivs. of phenylalanine ester free base.

DL-*Phenylglycylglycylglycine Ethyl Ester Hydrochloride*.—A solution of 2-thio-4-phenyl-5-thiazolidone (0·52 g.) in ethanol (10 c.c.) was treated with a mixture of glycylglycine ethyl ester (0·4 g., 1 equiv.) and triethylamine (0·25 g., 1 equiv.) in ethanol (10 c.c.). An immediate red colour was produced, which soon faded. After 25 minutes, the solution was acidified with 10*N*-ethanolic hydrogen chloride (1·5 c.c.) and cooled in ice with addition of a little ether. DL-*Phenylglycylglycylglycine ethyl ester hydrochloride* (0·3 g., 37%) was collected after 30 minutes, washed with acetone, and recrystallised from methanol–ether or –acetone in small laths, m. p. 239—240° (decomp.) (Found: C, 50·3; H, 5·9. $C_{14}H_{20}O_4N_3Cl$ requires C, 51·0; H, 6·1%). The above thiazolidone afforded a crystalline triethylamine salt with the base in acetone, which regenerated the thiothiazolidone on acidification in water.

Reaction of (I) *with Glycine Amide*.—Glycine amide (1·2 g.) in ethanol (50 c.c.) was added with stirring at 0° during 45 minutes to a solution of 2-thio-5-thiazolidone (1·05 g.) in ethanol (70 c.c.). The dithiocarbamate separated as a slightly pink, deliquescent solid. A portion was shaken with benzyl chloride in ether–water (8 hours) to give *N-dithiocarbobenzyloxyglycylglycine amide*, m. p. 116—118° (hydrate?) which recrystallised from ethyl acetate in rosettes of blades, m. p. 136° (Found: C, 49·1; H, 5·3; N, 13·7. $C_{19}H_{19}O_5N_3S_2$ requires C, 48·5; H, 5·05; N, 14·1%). When the above dithiocarbamate was dissolved in water and acidified with dilute hydrochloric acid, 2-thio-5-thiazolidone was produced in poor yield. When (I) was treated with glycine amide in acetone, the dithiocarbamate was superficially similar, but with benzyl chloride gave a low yield of a derivative, m. p. 195—196°.

Reaction of (I) *with Alanine Methyl Ester*.—Alanine methyl ester hydrochloride (1·4 g.) and triethylamine (2·02 g., 2 equivs.) were dissolved in methanol (15 c.c.), 2-thio-5-thiazolidone (1·33 g., 1 equiv.) was added, and the whole shaken. Heat was evolved and a pink solution obtained. This was acidified with 7*N*-methanolic hydrogen chloride (4 c.c.) and evaporated, and triethylamine hydrochloride (2·2 g.) removed by careful addition of acetone in which it was insoluble. The filtrate was analysed by paper chromatography (see final section), and shown to contain glycylalanine ester (yellow ninhydrin spot, R_F 0·37) as the main constituent, together with a little alanine ester (R_F 0·46), an unknown substance (R_F 0·55), and a glycine derivative (yellow ninhydrin spot, R_F 0·11). On storage overnight, the last substance separated in small amount, and had m. p. 195° (decomp.); it was sparingly soluble in ethanol. The filtrate was evaporated, the soluble hydrochlorides were extracted into water, and the bases liberated with potassium carbonate. Treatment with ethereal picric acid gave a small quantity of picrate, m. p. 93—125°, which could be recrystallised from ethanol and on chromatography on paper separated into a picric acid spot and a ninhydrin-reactive spot (R_F 0·55). It would thus appear to be the picrate of the unknown compound above.

Reaction of (I) *with Methionine Methyl Ester*.—2-Thio-5-thiazolidone (0·33 g.) was added to a mixture of methionine methyl ester hydrochloride (0·50 g., 1 equiv.) and triethylamine (0·50 g., 2 equivs.) in methanol (5 c.c.) and the whole shaken. After 20 minutes, 7*N*-methanolic hydrogen chloride (1 c.c.) was added, and the mixture evaporated and treated twice with acetone to give crops (total, 0·55 g.) of triethylamine hydrochloride. Paper chromatography of the filtrate showed it to be a mixture of the required glycyl-DL-methionine methyl ester hydrochloride (R_F 0·55) with unchanged methionine ester hydrochloride (R_F 0·75), 2-thio-5-thiazolidone dimer (reddish-purple spot, R_F 0·39), and glycine. Both the thiazolidone and diaminoacetoacetic acid to which it readily gives rise yield a characteristic reddish-purple ninhydrin spot at R_F 0·27 (glycine, 0·065), preceded by a " tail " in the former instance.

Reaction of (I) *with Valine Methyl Ester*.—2-Thio-5-thiazolidone (0·67 g.) was added to a mixture of valine methyl ester hydrochloride (0·84 g., 1 equiv.) and triethylamine (1·02 g., 2 equivs.) in dry methanol (10 c.c.) and the whole shaken. After 15—30 minutes, the reddish-brown solution was acidified with 7*N*-methanolic hydrogen chloride (2 c.c.) and evaporated to a gum, from which triethylamine hydrochloride was removed by two treatments with acetone. The filtrate contained largely glycyl-DL-valine methyl ester hydrochloride (R_F 0·66), together with valine ester (R_F 0·76) and a small amount of a substance having R_F 0·36 (yellow spot), together with a trace of glycine (R_F 0·10). On evaporation and treatment with ethyl acetate, the substance having R_F 0·36 separated; recrystallised from ethanol–ether, it had m. p. 178° (decomp.); analysis showed it to be glycine methyl ester hydrochloride (Found: C, 29·3; H, 6·4; N, 11·0. Calc. for $C_3H_8O_2NCl$: C, 28·7; H, 6·4; N, 11·15%). The filtrate, which darkened when kept overnight, did not yield the required peptide in crystalline condition.

The above synthesis was also carried out in chloroform solution, and in this case paper-chromatographic analysis of the product, after removal of the triethylamine hydrochloride, showed that glycine methyl ester was absent but that two other impurities (R_F 0·40 and 0·46) were present. The former had the characteristic reddish-purple ninhydrin reaction of the dimer of (I), and the latter was a glycyl derivative (yellow ninhydrin spot) the constitution of which is unknown. The oily glycylvaline ester hydrochlorides from this and the preceding experiment were combined and hydrolysed with 2*N*-sodium hydroxide. The solution was acidified with acetic acid and evaporated to dryness, whereafter treatment with ethanol caused separation of sodium chloride, which was removed. The filtrate was evaporated, dissolved in water, and chromatographed on a column of " Zeokarb 215 " as described in the succeeding paper. Crystalline glycyl-DL-valine, m. p. 239° (decomp.), chromatographically pure, was obtained in rather poor yield.

Reaction of (I) *with Phenylalanine*.—DL-Phenylalanine (0·83 g.) was dissolved in *N*-sodium hydroxide (10 c.c., 2 equivs.), 2-thio-5-thiazolidone (0·67 g., 1 equiv.) added, and the whole shaken to give a clear yellow solution. After 20 minutes this was acidified with concentrated hydrochloric acid (2·0 c.c.), and the heavy yellow oil which separated was removed and washed with water. Dissolution in acetone and seeding caused glycyl-DL-phenylalanine (0·28 g., 25%), m. p. 266° (decomp.), to separate rapidly; it recrystallised from aqueous ethanol in clusters of needles, m. p. 267° (decomp.). Similarly, when glycyl-DL-phenylalanine (0·96 g.) was shaken with a solution of potassium hydroxide (0·48 g.) in water (3·5 c.c.) and carbon disulphide (0·4 g.) for 2·2 hours, and the resulting clear reddish-orange solution acidified with concentrated hydrochloric acid, a heavy yellow oil was produced, which yielded glycylphenylalanine when dissolved in acetone.

Paper Chromatography.—For this work, unidimensional, descending chromatograms were run on Whatman No. 1 paper, with butanol–acetic acid (BuOH : AcOH : H_2O = 4 : 1 : 5) as the mobile phase. This solvent gave sharper spots and a cleaner paper, and was more pleasant to handle than phenol. Temperatures varied from about 15° to 25° on different occasions. The R_F values varied considerably with different papers, temperatures, etc., though their relative values remained more constant. Glycine was therefore arbitrarily selected as standard with R_F 0·10, and run with every chromatogram, the observed R_F values of other substances being computed proportionally. This correction was of less value with substances of high R_F values, which remained more constant under different experimental conditions and was therefore not applied in such cases (see tables). All spots were yellow initially with ninhydrin, but changed to the usual purple colour after keeping for some hours. In practice all the various crops of crystals, filtrates, etc., were analysed chromatographically though only certain significant determinations are reported. Values found are given in the annexed tables.

R_F *Values in butanol–acetic acid.*

	Free acid.	Me ester hydrochloride.	Et ester hydrochloride.	Amide.		Free acid.	Me ester hydrochloride.	Et ester hydrochloride.
Glycine	0·10	0·36	0·37	—	Glycylglycine	0·096	0·25	0·335
Alanine	0·18	0·46	—	—	Triglycine	0·078	—	0·25
Valine	0·42	0·53	—	—	Tetraglycine	0·053	—	0·18
Leucine	0·57	—	—	—	Pentaglycine	0·033	—	0·12
Norleucine	0·96	—	—	0·43	Glycylalanine	0·37	0·26	—
Phenylalanine	0·50	0·66	—	—	Glycylvaline	0·37	0·46	—
Methionine	0·33	0·52	—	—	Glycylphenylalanine	0·36	0·52	—
Tyrosine	0·54	0·50	—	0·31				
Glutamic acid	0·14	—	0·69 •	—				
Arginine	0·07	—	—	—				

Diglycylphenylalanine	0·30	Glycyl-leucine	0·42	Glycylnorleucine	0·38
Triglycylphenylalanine	0·23	Diglycyl-leucine	0·33	Diglycylnorleucine	0·30
Tetraglycylphenylalanine	0·18	Triglycyl-leucine	0·25	Triglycylnorleucine	0·23
Pentaglycylphenylalanine	0·14	Tetraglycyl-leucine	0·21	Tetraglycylnorleucine	0·17
Hexaglycylphenylalanine	0·11	Pentaglycyl-leucine	0·155	Pentaglycylnorleucine	0·12
Glycylmethionine methyl ester hydrochloride	0·38	Glycyltyrosine methyl ester hydrochloride	0·48	Polymer (MeOH, EtOH, pyridine) of (I)	0·52

• Diethyl ester hydrochloride.

We express our gratitude to Sir Ian Heilbron, D.S.O., F.R.S., for his very helpful interest, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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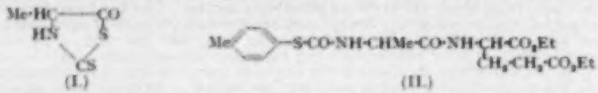
126. *Studies in the Azole Series. Part XXVIII. A New Method of Peptide Synthesis: Alanyl-peptides.*

By A. H. COOK and A. L. LEVY.

2-Thio-4-methyl-5-thiazolidone (I) has been used to provide alanyl-peptides in three different ways: (*a*) by the "ester" method described in the preceding paper, which gives lower yields than in the analogous glycine series; (*b*) by reaction with amino-acids in alkaline solution, followed by acidification with weak acids, preferably at an elevated temperature; and (*c*) by direct combination with amino-acids in hot acetic acid. Mixtures of the required peptide and its component amino-acids which result from (*b*) and (*c*) are conveniently separated on a column of cation-exchange resin.

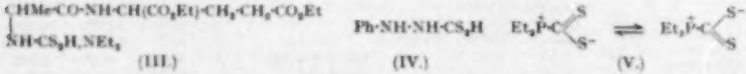
WHEN attempts were made to apply the general synthetic method described in the preceding paper for glycyl-peptides to the corresponding alanine derivative (I), the greater stability of (I) foreshadowed by earlier studies with model bases (Cook, Heilbron, and Levy, Part XXVI, *J.*, 1950, 642) precluded complete success. Thus, with alanine ester, the formation of alanylalanine ester was shown by the isolation of alanine anhydride but the yield was small. As with 2-thio-5-thiazolidone, a better result was obtained by coupling with a dipeptide ester, and alanylglycylglycine methyl ester hydrochloride was obtained in 40% yield by reaction with glycylglycine methyl ester and triethylamine in chloroform and then adding dry hydrogen chloride. This was later improved to 66% by acidifying with ethanolic acetic acid, followed by hydrogen chloride. As a model for the reaction with simple α-amino-esters, the condensation

of (I) with ethyl L-glutamate was studied; DL-alanyl-L-glutamic ester so obtained was isolated as its crystalline derivative, *ethyl* DL-*N*-[(*p*-*tolylthio*)*formyl*]*alanyl*-L-*glutamate* (II), in a yield of



(I.) (II.)

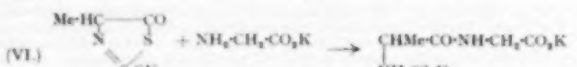
18%. The same overall yield also resulted from the four-stage synthesis: alanine methyl ester hydrochloride ⟶ *N*-[(*p*-tolylthio)formyl]alanine methyl ester ⟶ *N*-[(*p*-tolylthio)-formyl]alanine ⟶ *N*-[(*p*-tolylthio)formyl]alanyl chloride ⟶ (II) (cf. Ehrensvärd, *Nature*, **1947**, **157**, 500; Levy, *J.*, in the press).



(III.) (IV.) (V.)

It appeared from the work described in Part XXVI (*loc. cit.*) that opening of the ring in (I) by amines proceeded with excellent yield, but that acidification tended to cause reversion to (I) in substantial amount, even under anhydrous conditions. Some experiments were therefore carried out to see if carbon disulphide could be eliminated from (III) without the use of acids. It was shown in Part XXVI (*loc. cit.*) that the morpholine analogue of (III) readily lost its carbon disulphide as the highly insoluble morpholinium salt of 4-dithiocarboxymorpholine, but attempts to obtain this compound from (III) by treatment with two equivalents of morpholine were not successful. It is known that phenylhydrazine forms the stable compound (IV) with carbon disulphide (Fischer, *Annalen*, **1877**, **190**, 114), but preliminary experiments with 2-thio-5-thiazolidone indicated the consumption of four equivalents of phenylhydrazine and did not show promise. Triethylphosphine and carbon disulphide form a red addition compound (Hofmann, *Ber.*, **1880**, **13**, 1732), which may be formulated as the hybrid (V). It was hoped that the basic character of triethylphosphine would allow it to replace triethylamine in (III), when it might then detach carbon disulphide to give (V) and the required dipeptide ester. Indeed, when (I) was treated with equivalent amounts of ethyl glutamate and triethylphosphine in ethyl acetate, (V) was deposited in 50% of the theoretically possible amount during two hours, but the filtrate failed to yield (II) on treatment with tolyl chloro(thiolformate). However, replacing the triethylamine by triethylphosphine in the synthesis of glycylglycine ester discussed in the preceding paper resulted in a slight increase in yield, though the yield of glycyl-L-tyrosine ester was unaffected by a similar change. Some further properties of (V) are mentioned in the Experimental section.

As basic methods for removing carbon disulphide were unpromising, further study was given to acidification procedures. Following the action of boron trifluoride–ether on (III), (II) was obtained in a yield of 14% but, from the action of oxalic acid, only triethylamine oxalate could be isolated. Very slow acidification of (III) with hydrogen chloride in chloroform or in water (cf. Part XXVI, *loc. cit.*) did not yield any (II) on suitable treatment with *p*-tolyl chloro-(thiolformate).

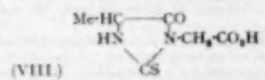


(VI.) (VII.)

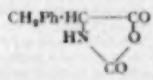
In view of these difficulties the possibility of effecting a useful interaction between 2-thio-5-thiazolidones and free amino-acids or peptides in aqueous solution was explored. The thio-thiazolidone (I) was dissolved in one equivalent of N-potassium hydroxide to give a solution of the monopotassium salt (VI) (pH 8·7), and a solution of glycine in one equivalent of N-potassium hydroxide added. The pH at once rose to 10·52 and then fell rapidly as the ring opened to give (VII), no further change appearing to take place after 10 minutes (pH 6·0). This fall in pH was to be expected during ring-fission, for not only is a strong base thereby consumed, but an acid ($^-NH{\cdot}CS_2H$) is liberated which is considerably stronger than the original mercaptothiazolone. As in the procedure developed for the model ammonium dithiocarbamate in Part XXVI (*loc. cit.*), the solution was titrated with N-hydrochloric acid during two hours, allowing time for loss of carbon disulphide to occur between each addition of acid. The "steps," however, were far less pronounced than in the model case, and (I) began to separate at pH 4·9 after only 15% of

the theoretical quantity of acid had been added, and continued till the end (pH 2·9), a yield of 68% being recovered. Paper chromatography of the filtrate showed that a little alanylglycine had been produced, together with much glycine and a moderate quantity of alanine. In an otherwise similar experiment, where an equivalent of boric acid was present, a 77% recovery of (I) was obtained and no alanylglycine could be detected in the filtrate. The absence of any unchanged (VI) in the solutions before acidification was shown by their stability to carbon dioxide, which liberates (I) from (VI), but not from (VII). In a slow titration of the crystalline barium salt of *N*-dithiocarboxyglycine with N-hydrochloric acid, carbon disulphide was liberated but the " steps " of pH drift were much less definite than with the ammonium salt of *N*-dithiocarboxyalanine amide; clearly the electrometric method is not so indicative of dithiocarbamic acid rupture in the case of peptides. A more promising result was obtained by acidifying (VII) with two equivalents of acetic acid, whereby the yield of (I) fell to 31% (45% on another occasion), paper chromatography showing that alanylglycine had been synthesised in fair quantity, though it was contaminated with glycine and alanine. Propionic acid gave a 28% recovery of (I), and very slow acidification with acetic acid yielded only a trace, but in each case the alanylglycine produced was mixed with its component amino-acids. The isolation of alanylglycine from such solutions by crystallisation proved difficult, owing to its tendency to form mixed crystals with the alanine and the glycine also present. This analytical problem was overcome, however, by " chromatography " on a column of the sulphonic acid-containing exchange-resin " Zeokarb 215 " (see Partridge and Westall, *Biochem. J.*, 1949, **44**, 418); the amino-acids were preferentially eluted by 0·1N-ammonia, followed immediately by the pure peptide. An attempt to use the column of resin to acidify (VII) and separate the products at the same time was not successful, for copious crystallisation of (I) took place and interfered with the flow of liquid.

Even milder conditions of acidification were achieved by opening the barium salt of (I) with barium glycine and decomposing the resulting barium salt of (VII) with carbon dioxide at 100°. Barium carbonate was precipitated, though incompletely even after 20 minutes, but the alanylglycine was once more contaminated with alanine and glycine, chromatography on " Zeokarb 215 " giving the crystalline peptide. When (VII) was treated with aqueous lead acetate, a yellow lead salt was clearly precipitated, which however with hydrogen sulphide yielded lead sulphide and the usual mixture of alanine, glycine, and peptide. Boiling the lead salt with water gave black lead sulphide, but the product was soluble in ethanol and was probably the 2-thiohydantoin (VIII) formed from an intermediate *iso*thiocyanate.



(VIII.)



(IX.)

A variation on the above techniques consisted in shaking a mixture of (I) and glycine with two equivalents of aqueous sodium hydrogen carbonate [whereupon the solids dissolved with evolution of carbon dioxide (neither, separately, gave carbon dioxide with the hydrogen carbonate)] and acidifying with two equivalents of acetic acid at 70°. Carbon disulphide was freely liberated, and no (I) separated on cooling. The method was also applicable to 2-thio-5-thiazolidone, which was in this way coupled with valine to give crystalline glycylvaline.

A third approach to the synthesis of alanyl-piptides from (I) was initiated by the observation that boiling equivalent quantities of (I) and glycine in water for a few moments led to substantial synthesis of alanylglycine. It was, of course, mixed with alanine and glycine, but no higher peptides were present, and the yield as judged from the relative intensity of the ninhydrin spots after chromatography of a sample of the product on paper was of the same order as that produced in the more elaborate experiments already described. When (I) was heated alone with water, it was hydrolysed completely to alanine without formation of any polymeric material. The effect of other solvents, and of different proportions of the reactants on the peptide synthesis was examined; the best procedure was to boil equimolecular amounts of (I) and glycine in acetic acid, which gave a mixture of alanylglycine and glycine (free from alanine). On a preparative scale, alanylglycine resulted in 48% yield from this reaction after " chromatography " on " Zeokarb 215." The analogous condensation with amino-acids other than glycine was less ready, though the synthesis of alanyl-glycylglycine, -alanine, -valine, and -arginine was demonstrated by paper chromatography. The direct method can also be used for α-amino-esters, and the syntheses of alanylglycine ester and alanylvaline ester by heating the components in acetic acid was established.

It was interesting to note that when anhydrocarboxyphenylalanine (IX) (Leuchs and Geiger, *Ber.*, 1908, **41**, 1721; Levy, *Nature*, in the press) was heated with glycine, tetraglycine, alanine, or valine in acetic acid, only the lower two or three polyphenylalanyl peptides were produced without any further polymerisation.

A list of R_F values of alanyl- and phenylalanyl-peptides is given at the end of the Experimental section.

Experimental.

Reaction of (I) *with Alanine Ester.*—2-Thio-4-methyl-5-thiazolidone (0·74 g.), DL-alanine methyl ester hydrochloride (0·70 g., 1 equiv.), and triethylamine (1·0 g., 2 equivs.) were dissolved in ethanol (10 c.c.) and kept at room temperature for 45 minutes. The solution was acidified with ethanolic hydrogen chloride and cooled in ice, and a crop of triethylamine hydrochloride removed; the filtrate was evaporated to dryness and a further crop precipitated by adding acetone. The filtrate was evaporated, and the residue rubbed with ethyl acetate to remove any thiothiazolidone. The remaining material was treated with saturated sodium hydrogen carbonate and extracted with chloroform, whereafter evaporation gave a basic-smelling oil which was kept at 100° in a vacuum to afford crystals of alanine anhydride, m. p. 275°.

Reaction of (I) *with Glycylglycine Methyl Ester.*—2-Thio-4-methyl-5-thiazolidone (0·73 g.), glycylglycine methyl ester hydrochloride (0·91 g., 1 equiv.), and triethylamine (1·0 g., 2 equivs.) were kept for 1·5 hours in chloroform (10 c.c.), and the solution was saturated with dry hydrogen chloride. A little ether was added. A semi-crystalline sludge obtained after 2 days was treated with ethanol–acetone to yield crude alanylglycylglycine methyl ester hydrochloride (0·5 g., 40%), m. p. 127—148°, which recrystallised from ethanol to give a product m. p. 153°, which was not depressed on admixture with material made according to Pacsu and Wilson (*J. Org. Chem.*, 1942, **7**, 126) and gave a single spot (R_F 0·25) on a paper chromatogram.

The same starting materials were kept for 30 minutes in ethanol (10 c.c.), acetic acid (0·65 c.c.) was added, and after 1·25 hours dry hydrogen chloride (2 equivs.) was passed in. Sufficient ethanol was added to re-dissolve a little triethylamine hydrochloride which separated, and the solution seeded with L-alanylglycylglycine methyl ester hydrochloride and kept overnight. The product which crystallised (0·84 g., 66%) had m. p. 158°, after contracting at 146°, and was essentially the same as the alanylglycylglycine methyl ester hydrochloride described above.

Ethyl DL-*N*-*[(p-Tolylthio)formyl]alanyl*-L-*glutamate.*—(*a*) 2-Thio-4-methyl-5-thiazolidone (0·73 g.) in chloroform (20 c.c.) was kept with ethyl L-glutamate (1·0 g., 1 equiv.) and triethylamine (0·5 g., 1 equiv.) for 1 hour. Dry hydrogen chloride was passed in, the solution concentrated in a vacuum, and the syrup dissolved in ethyl acetate, to which a little ether was then added. The solution was extracted with water (3 × 1—2 c.c.), and the aqueous phase treated with solid potassium carbonate at 0° and extracted with ether (3 times), some insoluble oil being rejected. The ethereal solution was dried ($MgSO_4$) and treated with *p*-tolyl chloro(thiolformate) (Levy, *J.*, in the press) until precipitation of triethylamine hydrochloride was complete. After 30 minutes, this was washed with water and with 2*N*-hydrochloric acid, dried, and evaporated to yield *ethyl* DL-*N*-*[(p-tolylthio)formyl]alanyl*-L-*glutamate* (0·4 g., 18%), m. p. 94°, which was recrystallised from ether without change of m. p. (Found: C, 56·8; H, 6·4; N, 6·4. $C_{20}H_{28}O_6S$ requires C, 56·6; H, 6·6; N, 6·6%).

(*b*) Alanine nitrile (Part XXVI) (23 g.) was added cautiously at 0° to a saturated solution of hydrogen chloride in methanol (120 c.c.), and kept overnight at room temperature. Ammonium chloride was filtered off, and the DL-alanine methyl ester hydrochloride (20·3 g.) crystallised (m. p. 155° (decomp.)) by adding ether to the filtrate. A further crop (10·2 g.; total yield, 66%), m. p. 152° (decomp.), was obtained by dilution with ethyl acetate and storage overnight at 0°. The ester hydrochloride (1·4 g.) in dry pyridine (3 c.c.) was treated, with cooling, with a solution of *p*-tolyl chloro(thiolformate) (1·87 g.) in pyridine (2 c.c.), and the whole stored overnight at 0°. The mixture was diluted with chloroform and extracted with 2*N*-hydrochloric acid, and the chloroform layer dried and evaporated, to yield *N*-*[(p*-tolylthio)formyl]alanine methyl ester (2·0 g., 80%), m. p. 83°. This ester (7·0 g.) was heated under reflux with acetic acid (25 c.c.) and concentrated hydrochloric acid (25 c.c.) for 15 minutes, water (25 c.c.) was added, and the mixture cooled to room temperature, to give *N*-*[(p*-tolylthio)formyl]-alanine (5·3 g., 83%), as flakes of m. p. 163°. This acid (1·2 g.) was boiled with benzene (30 g.), and phosphorus pentachloride (1·2 g.) added to the warm suspension, exothermic dissolution occurring. The benzene solution was concentrated under diminished pressure, and light petroleum added so long as the *N*-*[(p*-tolylthio)formyl]alanyl chloride (0·56 g., 44%) which crystallised (compact rosettes of spears, m. p. 102° (decomp.)) remained free from gum. The chloride (0·26 g.) in dry ether (15 c.c.) was cooled to 0°, and ethyl L-glutamate (0·40 g., 2 equivs.) added; after 1 hour at room temperature, the mixture was extracted with 2*N*-hydrochloric acid, dried, and evaporated to yield ethyl DL-*N*-*[(p*-tolylthio)formyl]alanyl-L-glutamate (0·31 g., 72%), m. p. 88°.

Experiments with Triethylphosphine.—Triethylphosphine (Hibbert, *Ber.*, 1906, **39**, 161) (0·59 g.) and ethyl glutamate (1·0 g.) in ethyl acetate (5 c.c.) were added to 2-thio-4-methyl-5-thiazolidone (0·73 g.) in ethyl acetate (5 c.c.). After 2 hours at room temperature, the deep-red prisms of triethylphosphine–carbon disulphide (0·5 g.) were removed, and the filtrate concentrated to small bulk. Treatment with *p*-tolyl chloro(thiolformate) (0·9 g.) and pyridine (2 c.c.), and working up in the usual way, yielded only *p*-tolyl dithiocarbonate, m. p. 95° (Found: C, 65·7; H, 5·4. Calc. for $C_{14}H_{14}OS_2$: C, 65·6; H, 5·14%).

2-Thio-5-thiazolidone (0·67 g.) in chloroform (10 c.c.) was treated with glycine ester (0·51 g., 1 equiv.) and triethylphosphine (0·6 g., 1 equiv.) in chloroform (3 c.c.). After 20 hours at room temperature, addition of ethanolic hydrogen chloride caused glycylglycine ethyl ester hydrochloride (0·72 g., 73%; m. p. 174—176°) to crystallise.

Triethylphosphine–carbon disulphide could be generated from its components in acetic acid, and was decomposed on contact with carbon tetrachloride. When warmed with glycine amide in ethanol, the

carbon disulphide was transferred and the amino-amide precipitated as its *N*-dithiocarboxy-derivative. Keeping *o*-aminobenzyl cyanide with triethylphosphine–carbon disulphide in chloroform for 4—5 days caused separation of yellow 2 : 4-dithio-5-phenylhydantoin, m. p. 264—265° (decomp.) (negative glyoxal test; cf. Cook, Heilbron, and Levy, *J.*, 1947, 1598).

Use of Boron Trifluoride.—2-Thio-4-methyl-5-thiazolidone (0·73 g.) in chloroform (10 c.c.) was treated with ethyl L-glutamate (1·0 g., 1 equiv.) and triethylamine (0·5 g., 1 equiv.), and boron trifluoride–ether (1·1 g., 2 equivs.) was added after 1 hour (heat evolved). After a further hour, ethanolic hydrogen chloride was added, and the mixture evaporated to a syrup and mixed with *p*-tolyl chloro(thioformate) (1·5 c.c.) in pyridine (10 c.c.). After 2·5 hours the solution was concentrated under diminished pressure, dissolved in ethyl acetate, and washed with 2N-sulphuric acid; drying and evaporating then yielded ethyl DL-*N*-[(*p*-tolylthio)formyl]alanyl-L-glutamate (0·3 g., 14%), m. p. 89—91°, after rubbing with a little ether.

Reaction of (I) *with Glycine in Alkaline Solution.*—Powdered 2-thio-4-methyl-5-thiazolidone (0·388 g.) was dissolved in N-potassium hydroxide (4·0 c.c., 1 equiv.) (pH then 8·7), and a solution of glycine (0·3 g., 1 equiv.) in N-potassium hydroxide (4·0 c.c.) added. The resulting pH changes were as follows:

pH	10·52	10·26	9·88	9·48	8·82	7·54	6·96	6·70
Time (mins.)	0	0·5	1	1·5	2	2·5	3	3·5
pH	6·55	6·44	6·38	6·27	6·18	6·14	6·05	6·03
Time (mins.)	4	4·5	5	6	7	8	10	11

The solution was then titrated slowly with N-hydrochloric acid (8·0 c.c.) during about 2 hours, the pH changes being followed for an average of 3 minutes after each addition. Initially, the rise was 0·2 pH unit during this period. (I) began to crystallise after 1·2 c.c. of acid had been added, the pH drift at this point being 0·15 unit in 3 minutes but becoming less as the titration proceeded. Finally, the mixture was extracted with ether, and the dried extracts were evaporated to yield (I) (0·40 g., 68%).

Experiment with Barium Glycine-N-dithiocarboxylate.—Glycine (1·5 g.) and barium hydroxide octahydrate (6·3 g.) were dissolved in water (15 c.c.) (warming), and shaken overnight with carbon disulphide (1·5 c.c.). On filtration of the solution from a little insoluble material, the required salt crystallised in dense, colourless prisms, m. p. above 300°. When titrated with N-hydrochloric acid (2 equivs.) during 1 hour, carbon disulphide was liberated, and the pH fell from 4·35 to 1·70. However, the rise in pH following each addition of acid was not marked, being about 0·2 unit in 3 minutes.

Use of Acetic Acid and a Cation-exchange Column.—2-Thio-4-methyl-5-thiazolidone (2·95 g.) was added to a solution of glycine (1·5 g., 1 equiv.) in N-potassium hydroxide (40 c.c., 2 equivs.), and the whole shaken. After 2 hours, acetic acid (2·4 g.) was added, and the 2-thio-4-methyl-5-thiazolidone which slowly separated (1·17 g.) was collected after an additional 2 hours. Extraction of the filtrate with ethyl acetate gave a further 0·15 g. of (I) (total recovery, 45%). The aqueous layer was evaporated to dryness in a vacuum, and the residue digested with several portions of hot ethanol to remove potassium acetate (the extract yielded a little glycine on cooling). The remaining material was dissolved in water (15 c.c.) (it contained glycine, alanylglycine, and alanine—paper chromatography) and run on to a column (25 cm. high in a 50-c.c. burette) of "Zeokarb 215" (~10 g., sieved to be retained between 40 and 60 B.S.S.). The "Zeokarb" was prepared for use by running through it (*a*) sodium chloride solution, (*b*) 4N-hydrochloric acid, and (*c*) distilled water. The zone of adsorption of the amino-acids and peptide was clearly visible, as the resin had changed from orange to yellow-brown, and the column was run with distilled water until this zone had grown to its full length. Development was then continued with 0·1N-ammonia, and the effluent collected in 5-c.c. fractions when a positive ninhydrin test was first given. The pH changes in the effluent were not a reliable guide to its composition, so 3 μl. of each fraction were run on a paper chromatogram for analysis. The first 7 fractions contained glycine and alanine, the eighth glycine, alanylglycine, and alanine, and the ninth to eleventh the peptide, with rapidly diminishing amounts of its component amino-acids, the last being pure alanylglycine. Fractions 10 and 11 were evaporated to dryness, and the residue crystallised from 50% ethanol–acetone to give pure alanylglycine (about 0·2 g.).

Use of Barium and Lead Salts.—Glycine (1·5 g.) in 0·34N-barium hydroxide (120 c.c.) was shaken for 45 minutes with 2-thio-4-methyl-5-thiazolidone (2·95 g.), and the solution (pH 8) treated with a stream of carbon dioxide (pH then 7), raising the temperature slowly. Precipitation of barium carbonate did not begin until the solution was almost boiling; this temperature was maintained for 45 minutes. The carbonate was removed (1·95 g.), and the filtrate (which still contained Ba^{++}) run on to a column of "Zeokarb 215" similar to that used above, except that resin retained between 100 and 120 B.S.S. was used. The overlap of amino-acids and peptide was less in this case, and 5 fractions containing pure alanylglycine were obtained on elution with ammonia, which yielded the solid peptide on evaporation.

(I) (0·735 g.) was shaken with glycine (0·375 g.) in N-potassium hydroxide (10 c.c.), and the resulting solution treated with aqueous lead acetate. The derivative was precipitated cleanly, yellow at first, but becoming almost white when the lead acetate was in excess. A portion of this lead derivative was suspended in water and treated with hydrogen sulphide. It dissolved to give a deep-brown solution, from which lead sulphide was precipitated after addition of a little acetic acid and boiling. The colourless filtrate contained glycine, alanylglycine, and alanine, as shown by paper chromatography. Another portion of the lead derivative was boiled with water for 15 minutes, being completely decomposed to give lead sulphide. The filtrate, however, contained only traces of ninhydrin-reactive materials, and on evaporation the solid residue was completely soluble in hot ethanol.

Use of Sodium Hydrogen Carbonate.—2-Thio-4-methyl-5-thiazolidone (0·73 g.), glycine (0·37 g.), and sodium hydrogen carbonate (0·85 g.) were shaken with water (10 c.c.) for 50 minutes, dissolving with evolution of carbon dioxide. The solution was heated to 70°, acetic acid (0·6 c.c.) was added, and the whole allowed to cool to room temperature. Carbon disulphide separated in small globules, no (I) was

recovered, and the solution contained a considerable proportion of alanylglycine, as shown by paper chromatography.

2-Thio-5-thiazolidone (0·67 g.), DL-valine (0·59 g.), and sodium hydrogen carbonate (0·84 g.) were shaken with water (10 c.c.) until dissolved, and no more carbon dioxide was evolved (~20 minutes). The pale pink solution was heated to 80°, and acetic acid (1·5 c.c.) added, after which the solution was evaporated to dryness in a vacuum. The residue was completely soluble in hot ethanol, though on storage overnight with ether a little glycine and valine separated. The filtrate was evaporated, dissolved in water, and run on to a column of "Zeokarb 215" (~15 g.; 100—120 B.S.S.) as in the previous examples. Development with 0·1N-ammonia gave 5 fractions (5 c.c.) containing glycine and valine, followed by 8 of pure glycylvaline. These eight were evaporated to give the solid peptide (0·4 g.), which was rubbed with methanol to remove a little colour and thereafter had m. p. 239° (decomp.).

Reactions with (I) *in Acetic Acid.*—2-Thio-4-methyl-5-thiazolidone (3·0 g.) and glycine (1·5 g.) were refluxed in acetic acid (85 c.c.) for 5 minutes, and the solvent was evaporated off in a vacuum. The syrupy residue was dissolved in water (10 c.c.), and filtered on to a column (23 × 1·5 cm.) of "Zeokarb 215" (~15 g.; 100—120 B.S.S.), which was washed through with water until acetic acid ceased to emerge and the yellow zone of adsorbed material extended for 18 cm. The column was then washed with 0·1N-ammonia, and the effluent collected in 10-c.c. fractions until the yellow zone reached the foot of the column. Fractions 1—5 contained glycine, 7—9 alanylglycine with diminishing quantities of glycine, and 10—25 alanylglycine, though with nos. 21—25 the ninhydrin spots on the paper chromatogram were slightly elongated, suggesting the presence of an impurity (perhaps alanylalanylglycine). Fractions 10—25 were evaporated to dryness and rubbed with ethanol, to give a slightly deliquescent sample of alanylglycine (1·4 g., 48%). Recrystallisation from 50% ethanol-acetone gave pure material (0·77 g.), m. p. 215° (decomp.).

Syntheses of alanylglycylglycine, etc. (theoretical section), were performed only on a micro-scale (1—2 mg.), with heating for about 1 minute and analysis of a little of the resulting acetic acid solution directly on a paper chromatogram. The new spot, additional to the amino-acid or peptide used, was assumed to be the alanyl derivative. The procedure was similar for the experiments with anhydro-*N*-carboxyphenylalanine, the first spot below the amino-acid being assumed to be the monophenylalanyl derivative, the next the diphenylalanyl, and so on.

R_F *Values of peptides.*

(The paper chromatograms were run with butanol–acetic acid as the mobile phase, as described in Part XXVII, and the R_F values are corrected for glycine = 0·1, unless otherwise stated.)

Alanylglycine	0·15	Phenylalanylglycine	0·34	(G = 0·07)
Alanylglycylglycine	0·107	Diphenylalanylglycine	0·55	,,
Alanylalanine	0·26	Triphenylalanylglycine	0·75	,,
Alanylvaline	0·43	Phenylalanyltetraglycine	0·155	,,
Alanylarginine	0·29	Diphenylalanyltetraglycine	0·37	,,
Alanylglycylglycine methyl ester HCl	0·25	Triphenylalanyltetraglycine	0·54	,,
Alanylvaline methyl ester	0·58	Phenylalanylalanine	0·53	,,
		Phenylalanylvaline	0·575	,,
		Diphenylalanylvaline	0·75	,,

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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127. *The Heats of Hydrolysis of the Benzoyl Halides.*

By A. S. CARSON, H. O. PRITCHARD, and H. A. SKINNER.

From measurements of the heats of hydrolysis of the benzoyl halides in aqueous acetone solutions, the following values (in kcal./mole) were obtained for the heats of formation at room temperature: $Q_f(C_6H_5{\cdot}COCl,\ liq.) = 39{\cdot}30$, $Q_f(C_6H_5{\cdot}COBr,\ liq.) = 25{\cdot}50$, $Q_f(C_6H_5{\cdot}COI,\ liq.) = 12{\cdot}55$.

These data are used to derive provisional values for the bond dissociation energies in a number of benzoyl–X molecules.

THIS paper reports values for the heats of hydrolysis of benzoyl chloride, bromide, and iodide, and is a continuation of studies on the hydrolysis heats of acid halides (Carson and Skinner, *J.*, 1949, 936; Pritchard and Skinner, *J.*, 1950, 272). The heats of hydrolysis of the benzoyl halides have not been measured previously, possibly because the reactions are slow to reach completion in a purely aqueous medium. Thermal difficulties arising from the tardiness of the aqueous hydrolyses may, however, be overcome by using aqueous acetone as the hydrolysis medium (cf. Pritchard and Skinner, *loc. cit.*). In a solvent obtained by mixing 400 c.c. of acetone

and 350 c.c. of water, the hydrolysis of benzoyl chloride was virtually complete in 30 minutes, and benzoyl bromide and iodide in the same solvent were hydrolysed in less than 15 minutes.

The heats of hydrolysis can be combined with known thermochemical data to give values for the heats of formation (Q_f) of the benzoyl halides. Apart from a single measurement of the heat of combustion of benzoyl chloride by Rivals (*Ann. Chim. Phys.*, **1897**, **7**, 541), corresponding to $Q_f(C_6H_5{\cdot}COCl, liq.) = 53{\cdot}2$ kcals., there are no data in the literature concerning the Q_f of the benzoyl halides.

Experimental.

Preparation of Compounds.—Benzoyl chloride (May and Baker) was purified by fractional distillation under reduced pressure. Benzoyl bromide was a pure Kahlbaum sample. Benzoyl iodide was made by Staudinger's method (*Ber.*, **1913**, **46**, 1417), *i.e.*, interaction of hydrogen iodide and benzoyl chloride; the crude product was shaken with mercury to remove traces of free iodine, and purified by careful fractionation under low pressure.

Thermal Measurements.—The heats of hydrolysis were measured by the same technique and apparatus used by Pritchard and Skinner (*loc. cit.*). The *observed* hydrolysis heats (listed in the following tables under $Q_{obs.}$) are the heats of the reactions :

$$C_6H_5{\cdot}COX\ (liq.) + H_2O(aq.\ acetone) \longrightarrow (C_6H_5{\cdot}CO_2H + HX)\ (aq.\ acetone) + Q_{obs.} \quad . \quad . \quad (1)$$

and differ from the heats of the purely aqueous hydrolyses (listed under $Q_{aq.}$), *viz.*,

$$C_6H_5{\cdot}COX\ (liq.) + H_2O\ (liq.) \longrightarrow C_6H_5{\cdot}CO_2H\ (c) + HX\ (aq.) + Q_{aq.} \quad . \quad . \quad (2)$$

by some small terms arising from the heat of solution and mixing of the benzoic acid and halogen acid in the aqueous acetone. These solution heats were measured separately as required.

In the tables of results, R_i and R_f refer to the initial and final values of the thermistor resistance, and $Q_{aq.}$ gives the heat of reaction (2) when the product is HX ($1000H_2O$).

Heat of hydrolysis of benzoyl halides.

Wt. of acid halide (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (liq.) (kcals.).	Wt. of acid halide (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (liq.) kcals.).
Benzoyl chloride.						Benzoyl bromide.					
3·5237	1710·2	1652·0	21·35	24·38	39·27	3·39	1746·8	1696·5	24·9	27·0	25·5
3·7900	1696·1	1634·4	21·23	24·26	39·39	3·0140	1748·8	1703·85	25·03	27·15	25·39
4·2940	1681·0	1611·65	21·34	24·37	39·28	3·5773	1744·0	1691·4	24·80	26·92	25·62
2·1719	1739·0	1701·6	21·36	24·39	39·26	3·0647	1746·0	1700·45	24·98	27·10	25·44
4·2040	1735·1	1663·75	21·31	24·34	39·31	3·0990	1747·0	1701·1	24·88	27·00	25·54
		Mean values	21·32	24·35	39·30			Mean values	24·92	27·04	25·50
Benzoyl iodide.											
5·4975	1711·7	1649·2	24·29	24·60	12·42	5·3296	1694·0	1635·45	24·00	24·31	12·71
5·9529	1700·15	1633·35	24·17	24·48	12·54	6·0524	1698·3	1631·15	24·24	24·55	12·47
5·1122	1692·2	1635·0	24·14	24·45	12·57	5·7887	1704·6	1640·4	24·11	24·42	12·60
								Mean values	24·16	24·47	12·55

The main reason for the differences between the $Q_{obs.}$ and $Q_{aq.}$ values arises from the negative solution heat (*ca.* −4·80 kcals./mole) of crystalline benzoic acid in the aqueous acetone; the $Q_{aq.}$ values, corresponding to reaction (2), refer to crystalline benzoic acid as one of the reaction products.

The calculated Q_f (liq.) values given in the final columns of the tables are based on assumed values for the heats of formation of the halogen hydracids ("Selected Values of Chemical Thermodynamic Constants," National Bureau of Standards, Washington, 1948) and on $Q_f(C_6H_5{\cdot}CO_2H, c.) = 92{\cdot}06$ kcals./mole (Jessup, *J. Res. Nat. Bur. Stand.*, **1942**, **29**, 247). It may be remarked that the Q_f value of 53·2 kcals., derived from Rivals's heat of combustion of benzoyl chloride, corresponds to a heat of hydrolysis ($Q_{obs.}$) of only 7·4 kcals.

Discussion.

The Q_f values obtained from these experiments refer to the *liquid* state at room temperature. Data are not available on the heats of vaporisation of the benzoyl halides, but a rough estimate of these can be made by use of Trouton's rule. The results are summarised below :

	$C_6H_5{\cdot}COCl$.	$C_6H_5{\cdot}COBr$.	$C_6H_5{\cdot}COI$.
Q_f (liq.) (kcals.)	39·30	25·50	12·55
Q_f (gas) (kcals.)	28·9	14·7	1·3
$\lambda_{vap.}$ (assumed) (kcals.)	10·4	10·8	11·2

The Q_f (gas) values may be correlated with the bond dissociation energies $D(C_6H_5{\cdot}CO{-}X)$ by the equation

$$D(C_6H_5{\cdot}CO{-}X) = Q_f(C_6H_5{\cdot}COX) - Q_f(X) - Q_f(C_6H_5{\cdot}CO) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where the terms in Q_f are heats of formation from elements in standard states, and $D(C_6H_5{\cdot}CO{-}X)$ is the heat of the reaction $C_6H_5{\cdot}CO + X \longrightarrow C_6H_5{\cdot}COX$. The term $Q_f(C_6H_5{\cdot}CO)$ in equation (3) cannot be determined directly, but can be evaluated if both $D(C_6H_5{\cdot}CO{-}X)$ and $Q_f(C_6H_5{\cdot}COX)$ are known for *one* specific $C_6H_5{\cdot}COX$ compound. In this event, equation (3) can be generally applied to determine D(benzoyl–X) in other benzoyl derivatives.

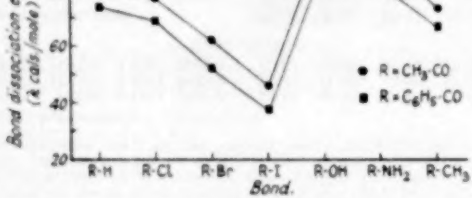
Apart from the kinetic studies of Butler and Polanyi (*Trans. Faraday Soc.*, 1943, **39**, 19) on the pyrolytic decomposition of benzoyl iodide, there are no experimental data from which D values in benzoyl–X can be assessed. Butler and Polanyi gave $D(C_6H_5{\cdot}CO{-}I) = 43{\cdot}9$ kcals., but this result was not claimed to be of high accuracy. In general, the D(R–I) values given by Butler and Polanyi seem to be accurate within limits of ± 5 kcals., and for the purpose of the present paper we shall adopt a value of $D(C_6H_5{\cdot}CO{-}I) = 42$ kcals. $(\pm x)$, where x is probably less than 5 kcals. This provisional $D(C_6H_5{\cdot}CO{-}I)$ value corresponds to Q_f(benzoyl) $= -15{\cdot}2 \pm x$ kcals., which, substituted into equation (3), leads to the following D values in the listed benzoyl–X compounds:

Bond.	Q_f (gas).	Q_f (X).	$D(C_6H_5{\cdot}CO{-}X)$ $(\pm x)$.	Bond.	Q_f (gas).	Q_f (X).	$D(C_6H_5{\cdot}CO{-}X)$ $(\pm x)$.
$C_6H_5{\cdot}CO{-}H$ ...	11·2 [a]	−52·0	78·4 [a]	$C_6H_5{\cdot}CO{-}OH$	68 [a]	−10·0	93·2 [a]
$C_6H_5{\cdot}CO{-}Cl$ ...	28·9 [b]	−29·0	73·1	$C_6H_5{\cdot}CO{-}NH_2$	30 [c]	−41·0 [d]	86·2 [a]
$C_6H_5{\cdot}CO{-}Br$ ...	14·7 [a]	−26·7	56·6	$C_6H_5{\cdot}CO{-}CH_3$	24 [e]	−32·1	71·3 [a]
$C_6H_5{\cdot}CO{-}I$ ...	1·3 [b]	−25·5	42	$C_6H_5{\cdot}CO{-}C_6H_5$	−13 [a]	−69·8	72 [a]

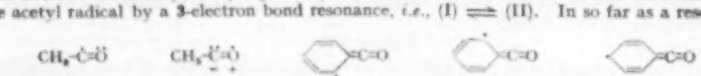
[a] Based on data listed by Wheland ("The Theory of Resonance," John Wiley, 1944). [b] This research. [c] Kharasch (*J. Res. Nat. Bur. Stand.*, 1929, **2**, 407). [d] Szwarc (*J. Chem. Physics*, 1949, **17**, 505). [e] Beckers (*Bull. Soc. chim. Belg.*, 1931, **40**, 518); Neumann and Volker (*Z. physikal. Chem.*, 1932, **161**, *A*, 33).

[a] Asterisked values are doubtful because of uncertainties in the heats of formation Q_f (gas).

The value given for $D(C_6H_5{\cdot}CO{-}H)$ is a relatively "low" value for a C–H bond dissociation energy. Compared with the C–H bonds in ethylene or benzene, both of which are of the same sp^2–s hybrid type, $D(C_6H_5{\cdot}CO{-}H)$ is smaller by some 20 or more kcals. The weakness of the benzoyl–H bond is strongly suggestive of a powerful resonance stabilisation in the benzoyl radical.



Roberts and Skinner (*Trans. Faraday Soc.*, 1949, **45**, 339) commented on the weakness of the C–H bond in acetaldehyde, $D(CH_3{\cdot}CO{-}H) \approx 80$ kcals., and attributed this to a stabilisation in the acetyl radical by a 3-electron bond resonance, *i.e.*, (I) $\rightleftharpoons$ (II). In so far as a resonance

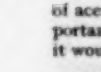


(I.) (II.) (III.) (IV.) (V.)

stabilisation of this type occurs in $CH_3{\cdot}\dot{C}O$, it should similarly be present in the benzoyl radical, and from this point of view the low value of $D(C_6H_5{\cdot}CO{-}H)$ should be compared with the low value of $D(CH_3{\cdot}CO{-}H)$. Indeed, one might expect the $C_6H_5{\cdot}\dot{C}O$ radical to be resonance-stabilised to a greater extent than $CH_3{\cdot}\dot{C}O$, in that the excited structures of the types (III), (IV), and (V) in relation to $C_6H_5{\cdot}\dot{C}O$ are probably more significant than the structures $H^+CH_2{=}C{=}O$ in relation to $CH_3{\cdot}\dot{C}O$.

In the figure, bond-dissociation energies in a series of benzoyl–X and acetyl–X compounds

are plotted together,* to bring out their close similarity in respect of varying X. The present values do not correspond to a strictly constant difference, ΔD, where $\Delta D = D(CH_3{\cdot}CO{-}X) - D(C_6H_5{\cdot}CO{-}X)$, although these differences are approximately equal. Some of the D values are, however, based on not very reliable combustion-heat data, and most involve uncertainties of the order ± 1 or ± 2 kcals. in the heats of vaporisation, so that the trends in ΔD may be partly obscured by errors in the data we have used. Nevertheless, the data are sufficient to show that the factors influencing the strength of acetyl–X bonds are similarly operative in benzoyl–X. For example, if one accepts the importance of back-co-ordination, as represented by the resonance structure (VI) in acetyl chloride, it would seem to be no less important in benzoyl chloride.



(VI.)

The authors thank Professor M. G. Evans, F.R.S., for his interest in this work, and Mr. T. Charnley for some valuable assistance in the preparation of benzoyl iodide. One of them (H. O. P.) thanks the D.S.I.R. for a maintenance grant.

MANCHESTER UNIVERSITY. [*Received, November 18th*, 1949.]

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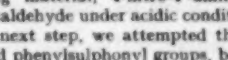
128. *Studies on Antibiotics. Part IV.*† *Substituted ω-Phenylsulphonylacetophenones, Bisphenylthio- and Bisphenylsulphonyl-alkane Derivatives.*

By F. BERGEL, A. L. MORRISON, and H. RINDERKNECHT.

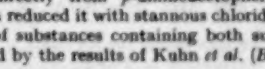
In continuation of previous work (Rinderknecht, Ward, Bergel, and Morrison, *Biochem. J.*, 1947, **41**, 463), the preparation of substances containing a combination of substituted benzoyl and phenylsulphonyl groups was undertaken with the aim (unfulfilled) of finding effective antibacterial agents. Thus various aromatic β-keto-sulphones (II; $n = 1$), β-bisthio-compounds (III), and β-disulphones (IV) were synthesised.

In Part II of our series "Studies on Antibiotics" (*Biochem. J.*, 1947, **41**, 463) we showed that benzoylacrylic acid and its 4-chloro- and 2 : 4-dichloro-derivatives possessed marked activities *in vitro* against Gram-positive and Gram-negative organisms. We deduced in agreement with Geiger and Conn (*J. Amer. Chem. Soc.*, 1945, **67**, 112) that the presence of the grouping $-CO-C{=}C-$ might be a pre-requisite for such antibacterial properties (cf. also Geiger, *Arch. Biochem.*, 1948, **16**, 423). In continuation of this work we prepared some time ago *p*-acetamidobenzoylacrylic acid (I; $R_1 = Ac$, $R_2 = CO_2H$) (cf. B.P. 588,108/1944) which we failed to hydrolyse to the 4-amino-compound. Since then, two groups of American workers, Papa, Schwenk, Villani, and Klingsberg (*J. Amer. Chem. Soc.*, 1948, **70**, 3356) and Cramer, Schroeder, Moran, Nield, Edwards, Sarowsky, and Puetzer (*J. Amer. Pharm. Assoc., Sci. Edn.*, 1948, **37**, 439), announced the preparation of this acetamido-compound among other derivatives of benzoylacrylic acid. We wished to replace the carboxyl group of benzoylacrylic acid by another structure and synthesised, independently of Marrian, Russell, and Todd (*J.*, 1947, 1419) 4 : 4′-diaminochalkone (I; $R_1 = H$, $R_2 = p\text{-}NH_2{\cdot}C_6H_4$); but unlike these authors we prepared the starting material, 4-nitro-4′-aminochalkone, directly from *p*-aminoacetophenone and *p*-nitrobenzaldehyde under acidic conditions and then reduced it with stannous chloride.

As the next step, we attempted the synthesis of substances containing both substituted benzoyl and phenylsulphonyl groups, being prompted by the results of Kuhn *et al.* (*Ber.*, 1942, **75**, 711; 1943, **76**, 405).



(I.)



(II.)

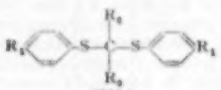
Whilst we failed to synthesise amino-substituted α-keto-sulphones (II; $n = 0$) in spite of the claims by Kohler and Macdonald (*Amer. Chem. J.*, 1909, **22**, 225) for unsubstituted ones, we succeeded in making a number of representatives of β-keto-sulphones (II; $n = 1$) by treating sodium acetamido- or acetamidomethyl-benzenesulphinate with ω-chloroacetophenone substituted by acetamido-, hydroxy-, or chloro-groups. In this we followed Troeger and Beck (*J. pr. Chem.*, 1913, [ii], **87**, 289) who prepared several arylsulphonylacetophenones, but none with amino- or aminomethyl substituents. After hydrolysis of the acetamido-

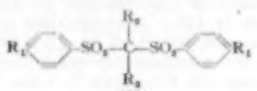
* The benzoyl–X dissociation energies in this figure are based on $x = -5$ kcals., in order to separate the two curves sufficiently to show their form more clearly.

† Part III, *Chem. and Ind.*, 1949, 640.

derivatives, p-*amino*- (II; $n = 1$, $R_1 = NH_2$, $R_2 = H$, $R_3 = NH_2$), and p-*hydroxy*-ω-p'-*amino*-*phenylsulphonylacetophenone* (II; $n = 1$, $R_1 = OH$, $R_2 = H$, $R_3 = NH_2$) and the corresponding p'-*aminomethyl* compounds ($R_3 = CH_2{\cdot}NH_2$) were obtained. Encouraged by the report on the antitubercular activity of 2 : 4 : 2' : 4'-tetrachlorobenzophenone (Freedlander, *Proc. Soc. Exp. Biol. Med.*, 1942, **51**, 153; *Amer. Rev. Tubercul.*, 1944, **49**, 543) and the high effect of our 2 : 4-dichlorobenzoylacrylic acid *in vitro*, we added to our list of compounds 2 : 4-*dichloro*-ω-p'-*aminophenylsulphonylacetophenone* (II; $n = 1$, $R_1 = R_2 = Cl$, $R_3 = NH_2$) and the corresponding p'-*aminomethyl* analogue ($R_3 = CH_2{\cdot}NH_2$).

When, in the general structure (II; $n = 1$), the carbonyl group is exchanged for another sulphonyl group, substances (IV) emerge which can be prepared from β-bisthio-compounds (III) by oxidation. Methods for the synthesis of aliphatic and unsubstituted aromatic representatives of this series were described by Escales and Baumann (*Ber.*, 1886, **19**, 2814), Fromm (*Annalen*, 1889, **253**, 135), and Otto and Muehle (*Ber.*, 1895, **28**, 1121) who either condensed thiols with aldehydes or ketones or treated the sodium salt of thiols with dihalogeno-compounds. Concerning acylamino- or amino-derivatives of aromatic analogues, there are two American papers available: in the earlier, Waldron and Reid (*J. Amer. Chem. Soc.*, 1923, **45**, 2399) claimed the preparation of (III; $R_1 = NH_2$, $R_2 = R_3 = H$) by reduction of the corresponding dinitro-derivative; in the more recent, Cutter, Danielson, and Golden (*ibid.*, 1945, **67**, 1051, published while our investigation was in progress) described the synthesis of bis-*p*-acetamidophenylthiomethane (III; $R_1 = NHAc$, $R_2 = R_3 = H$) from *p*-acetamido-thiophenol or its sodium salt with formaldehyde or methylene iodide, respectively. This they also oxidised to (IV; $R_1 = NHAc$, $R_2 = R_3 = H$) which was hydrolysed to the diamino-disulphone (IV; $R_1 = NH_2$, $R_2 = R_3 = H$). In addition to preparing the same compounds, we succeeded in hydrolysing the bis-*p*-acetamidophenylthiomethane to Waldron and Reid's diamino-derivative which formed light ochre-coloured, and not, as they say, red, crystals; we also synthesised certain analogues. For instance, paraldehyde and *p*-acetamidothiophenol gave 1 : 1-*bis*-p-*acetamidophenylthioethane* (III; $R_1 = NHAc$, $R_2 = Me$, $R_3 = H$) which by alkaline hydrolysis, but not by acid (which caused decomposition), yielded the corresponding *diamino*-compound and by oxidation gave (IV; $R_1 = NHAc$, $R_2 = Me$, $R_3 = H$). This sulphone on treatment with alcoholic potassium hydroxide gave 1 : 1-*bis*-p-*aminophenylsulphonylethane* (IV; $R_1 = NH_2$, $R_2 = Me$, $R_3 = H$). By use of acetone or


(III.)


(IV.)

p-nitrobenzaldehyde in the first step of the synthesis 2 : 2-*bis*-p-*acetamidophenylthiopropane* (III; $R_1 = NHAc$, $R_2 = R_3 = Me$) and p-*nitro*-ω,ω-*bis*-p'-*acetamidophenylthiotoluene* (III; $R_1 = NHAc$, $R_2 = p\text{-}NO_2{\cdot}C_6H_4$, $R_3 = H$), respectively, were obtained. Finally in this group of compounds the use of dichloroacetic acid led to the formation of di-(*p*-acetamidophenyl-thio)acetic acid (III; $R_1 = NHAc$, $R_2 = CO_2H$, $R_3 = H$) and the corresponding *diamino*-derivative.

When we approached the synthesis of aminomethyl derivatives of (III) and (IV), we found that the preparation of *p*-acetamidomethylthiophenol, wanted as starting material, offered difficulties in view of its great solubility in water. However, three methods were tried which led eventually to success. First, the sodium salt from crude, oily *p*-acetamidomethylthiophenol was condensed with methylene dichloride to give *bis*-p-*acetamidomethylphenylthiomethane* (III; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$). This was oxidised in the usual way to (IV; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$) which hydrolysed with acid to the *bis*-p-*aminomethylphenyl-sulphonylmethane dihydrochloride* (IV; $R_1 = CH_2{\cdot}NH_2{,}HCl$, $R_2 = R_3 = H$). Although in our second approach p-*benzamidomethylthiophenol*, unlike the acetyl compound, formed sparingly soluble crystals and could be condensed to give *bis*-p-*benzamidomethylphenylthiomethane* (III; $R_1 = CH_2{\cdot}NHBz$, $R_2 = R_3 = H$), the oxidation of this compound to (IV; $R_1 = CH_2{\cdot}NHBz$, $R_2 = R_3 = H$) was difficult, and further neither the bisthio-compound nor the disulphone could be hydrolysed under alkaline or acidic conditions to the free aminomethyl derivatives. The third and best method used succinimido-derivatives. Succinbenzylamide reacted with chlorosulphonic acid to give p-*succinimidomethylbenzenesulphonyl chloride*, which was reduced in the usual way. p-*Succinimidomethylthiophenol*, thus formed, condensed with formaldehyde,

and the product, *bis*-p-*succinimidomethylphenylthiomethane* (III; R_1 = succinimidomethyl, R_2 = R_3 = H), was oxidised with hydrogen peroxide to the *disulphone* (IV; R_1 = succinimidomethyl, R_2 = R_3 = H). When this bisthio-compound was heated with dilute aqueous sodium hydroxide, and the solution was treated with potassium permanganate, a compound was isolated, very likely the succinamic acid derivative, which, on the one hand, with warm dilute hydrochloric acid gave the succinimido-disulphone described above, and, on the other hand, after prolonged heating with aqueous potassium hydroxide produced *bis*-p-*aminomethylphenylsulphonylmethane*, giving a dihydrochloride and a diacetyl derivative identical with those derived from the disulphone (IV; R_1 = CH_2·NH_2, R_2 = R_3 = H) prepared from crude acetamidomethylthiophenol.

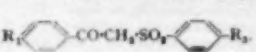
Preliminary bacteriological examination *in vitro* of some of the compounds just mentioned did not disclose any outstanding antibacterial activity.

Experimental.

4 : 4'-*Diaminochalkone* (I; R_1 = H, R_2 = *p*-NH_2·C_6H_4).—*p*-Nitrobenzaldehyde (4·5 g.) and *p*-aminoacetophenone (4·05 g.) were dissolved in ethanol (100 ml.). After saturation of the solution with gaseous hydrogen chloride under ice-cooling, crystalline material separated overnight and was filtered off and dissolved in 2*N*-hydrochloric acid (*ca.* 700 ml.). On cooling, the hydrochloride of 4-nitro-4'-aminochalkone crystallised. It was suspended in methanol (100 ml.) and aqueous ammonia was added, whereupon orange-coloured 4-nitro-4'-aminochalkone was obtained; recrystallised from pyridine or chloroform, it had m. p. 221—223° (Found: C, 66·7; H, 4·5; N, 10·1. Calc. for $C_{15}H_{12}O_3N_2$: C, 67·2; H, 4·5; N, 10·4%). This compound (4·0 g.) in saturated alcoholic hydrochloric acid (40 ml.) was reduced with stannous chloride (11·0 g.). When warmed, a yellow solution was obtained which, after storage overnight, deposited a red tin salt. This was dissolved in water and decomposed with a solution of sodium acetate. The diaminochalkone was extracted with butanol and, obtained pure by recrystallising from aqueous acetone, melted at 181—183° (Found: C, 70·4; H, 6·3; N, 11·2. Calc. for $C_{15}H_{14}ON_2.H_2O$: C, 70·4; H, 6·3; N, 10·9%).

ω*-p-*Substituted Phenylsulphonylacetophenones (II; n = 1).—A number of compounds of this series was prepared by the general method of Troeger and Beck (*loc. cit.*) from ω-chloroacetophenones and sodium salts of *p*-acetamidophenylsulphinic (cf. *Org. Synth.*, Coll. Vol. I, p. 7) and *p*-acetamidomethylphenylsulphinic acid (cf. F.I.A.T. Final Report No. 915, 52; Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099). The acetyl derivatives were hydrolysed by heating them to the b. p. with 2*N*-hydrochloric acid until a clear solution was obtained. Addition of sodium carbonate solution precipitated the free amino-compounds which were recrystallised from the appropriate solvents. These compounds are listed in the table.

ω-Arylsulphonylacetophenones.



R_1.	R_2.	R_3.	M. p.	Solvent for recrystn.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Required, %. C.	Required, %. H.	Required, %. N.
NHAc	H	NHAc	271—274°	A	$C_{18}H_{18}O_4N_2S$	57·6	5·0	—	57·7	4·8	—
NH_2	H	NH_2	225—227	B	$C_{14}H_{14}O_2N_2S$	57·8	4·9	—	58·0	4·8	—
NHAc	H	CH_2·NHAc	203—205	A	$C_{18}H_{20}O_4N_2S$	59·2	5·3	7·2	58·8	5·2	7·2
NH_2	H	CH_2·NH_2	185—186	B	$C_{15}H_{16}O_2N_2S$	59·2	5·4	9·3	59·2	5·3	9·2
OH	H	NHAc	235—238	A	$C_{16}H_{15}O_4NS$	—	—	4·3	—	—	4·2
OH	H	NH_2	225—226	C	$C_{14}H_{13}O_3NS$	57·8	4·6	5·2	57·8	4·5	4·8
OH	H	CH_2·NHAc	168—173	C	$C_{17}H_{17}O_4NS$	58·7	5·2	4·2	58·8	4·8	4·0
OH	H	CH_2·NH_2	203 [a]	B	$C_{15}H_{15}O_3NS$	58·8	5·9	4·7	59·0	4·9	4·6
Cl	Cl	NHAc	164—167	C	$C_{16}H_{13}O_4NCl_2S$	49·8	3·2	—[c]	49·8	3·4	—[c]
Cl	Cl	NH_2	172—175	C	$C_{14}H_{11}O_3NCl_2S$	48·5	3·1	4·5	48·6	3·2	4·1
Cl	Cl	CH_2·NHAc	125—127	C	$C_{17}H_{15}O_4NCl_2S$	51·3	3·3	—[b]	51·0	3·8	—[b]
Cl	Cl	CH_2·NH_2	194—195	D	$C_{15}H_{13}O_3NCl_2S$	50·4	3·7	3·7	50·3	3·6	3·9

[a] With decomp.
Solvents: A, acetic acid; B, aqueous ethanol; C, ethanol; D, pyridine.
[b] Found: Cl, 18·3. Required: Cl, 18·4%. [c] Found: Cl, 17·9. Required: Cl, 17·8%.

Bis*-p-*aminophenylthiomethane (III; R_1 = NH_2, R_2 = R_3 = H).—Bis-*p*-acetamidophenylthiomethane (3·8 g.) was hydrolysed by hot 2*N*-sulphuric acid (100 ml.), the sulphate of the diamine crystallising on cooling. The base itself, obtained by neutralisation with sodium carbonate solution, formed light ochre-coloured crystals when recrystallised from ethanol. It melted at 98—100° (Found: N, 11·1. Calc. for $C_{13}H_{14}N_2S_2$: N, 10·7%).

1 : 1-*Bis*-p-*acetamido- and* -p-*amino-phenylthioethane* (III; R_1 = NHAc or NH_2, R_2 = Me, R_3 = H).—To *p*-acetamidothiophenol (6·68 g.) and chloroform (70 ml.), paraldehyde (0·88 g.) was added and the mixture was saturated with hydrogen chloride. The oily material which separated after 24 hours was treated with boiling water, a white solid being formed. Recrystallisation from ethyl acetate gave pure **1 : 1-*bis*-p-*acetamidophenylthioethane***, m. p. 191—193° (5·9 g.) (Found: N, 7·9. $C_{18}H_{20}O_2N_2S_2$ requires N, 7·8%).

Hydrolysis of the above acetyl derivative (3·4 g.) by refluxing in 10% alcoholic potassium hydroxide

solution (34 ml.) for 3 hours yielded only a small amount of the desired material, most of the product being unchanged acetyl derivative. The *bisthio-ethane* was separated from the starting material by dissolution in 2*N*-hydrochloric acid and then basification, and was obtained pure by recrystallisation from alcohol, whereafter it melted at 81—83° (Found: C, 61·0; H, 5·8; N, 10·5. $C_{12}H_{16}N_2S_2$ requires C, 60·8; H, 5·8; N, 10·1%).

1 : 1-*Bis*-p-*acetamido- and* -p-*amino-phenylsulphonylethane* (IV; R_1 = NHAc or NH_2, R_2 = Me, R_3 = H).—The above bisthio-ethane (III; R_1 = NHAc, R_2 = CH_3, R_3 = H) (5·8 g.) was dissolved in glacial acetic acid (40 ml.), and 60% (w/v) hydrogen peroxide (12 ml.) was added at 40°. After 24 hours at room temperature, the precipitate which had formed was filtered off, washed with water, and recrystallised from 60% aqueous acetic acid (120 ml.), the *diacetyl* compound being obtained pure as a light ochre-coloured compound with m. p. 263—266° (3·7 g.) (Found: N, 6·5. $C_{12}H_{16}O_6N_2S_2$ requires N, 6·6%).

Heating this acetyl compound (2 g.) with a solution of potassium hydroxide (5 g.) in ethanol (14 ml.) and water (7 ml.) under reflux for 4 hours yielded a potassium salt, very sparingly soluble in water, which, on treatment with dilute hydrochloric acid, gave the *diamine*, m. p. 202—204° [recrystallised from ethanol (150 ml.)] (1 g.) (Found: C, 49·9; H, 4·9; N, 8·6. $C_{14}H_{16}O_4N_2S_2$ requires C, 49·4; H, 4·7; N, 8·2%).

2 : 2-*Bis*-p-*acetamidophenylthiopropane* (III; R_1 = NHAc, R_2 = R_3 = Me).—*p*-Acetamidothiophenol (3·4 g.) was condensed with acetone (0·58 g.) in chloroform (35 ml.) by passing in hydrogen chloride. The product which separated overnight was worked up in the usual manner to give the *bisthio-propane*, m. p. 224—225° (recrystallised from ethanol several times) (Found: N, 7·6. $C_{19}H_{22}O_2N_2S_2$ requires N, 7·5%).

p-*Nitro-αα-bis-p′-acetamidophenylthiotoluene* (III; R_1 = NHAc, R_2 = *p*-NO_2-C_6H_4, R_3 = H).—*p*-Acetamidothiophenol (3·4 g.) was condensed with *p*-nitrobenzaldehyde (1·51 g.) in chloroform (150 ml.) in the usual manner by passing in hydrogen chloride. The *bisthio-toluene* was obtained pure by recrystallising it from glacial acetic acid and melted at 221—223° (Found: N, 9·15. $C_{23}H_{21}O_4N_3S_2$ requires N, 9·0%).

Di-(p-*acetamido- and* -p-*amino-phenylthio)acetic acid* (III; R_1 = NHAc or NH_2, R_2 = CO_2H, R_3 = H).—Sodium *p*-acetamidothiophenoxide, prepared from sodium (0·7 g.) in ethanol (20 ml.) and the thiol (3·34 g.), was refluxed together with dichloroacetic acid (1·5 g.) for 2 hours. The residue of *bis-p-acetamido-acid*, after removal of the solvent by distillation, was treated with dilute hydrochloric acid and water and then sodium hydrogen carbonate, liberated from the resulting sodium salt by dilute hydrochloric acid, and finally recrystallised from ethanol, showing m. p. 230—235° (decomp.) (Found: N, 7·1. $C_{18}H_{18}O_6N_2S_2$ requires N, 7·2%). This derivative (2·5 g.) was hydrolysed by heating it under reflux for 4 hours with 2*N*-hydrochloric acid (75 ml.). On concentration, a crystalline hydrochloride separated out. This was dissolved in water and the solution neutralised carefully with dilute aqueous ammonia to give the *diamine* which, recrystallised from aqueous alcohol, melted at 117—119° (Found: N, 9·1. $C_{14}H_{14}O_2N_2S_2$ requires N, 9·2%).

Bis-p′-acetamidomethylphenylthiomethane (III; R_1 = CH_2·NHAc, R_2 = R_3 = H).—*p*-Acetamidomethylbenzenesulphonyl chloride, prepared from *N*-benzylacetamide (48 g.), was dissolved in a mixture of alcohol (30 ml.) and water (100 ml.), zinc dust (100 g.) and concentrated hydrochloric acid (150 ml.) were added in portions with stirring and cooling, and the reaction mixture was finally heated to 80° for 5 minutes. After being cooled the solution was saturated with ammonium sulphate, and the oil which separated was dissolved in amyl alcohol and washed with a small amount of cold water. After removal of the amyl alcohol under reduced pressure, the residue was added to a mixture of ethanol (30 ml.), sodium (1·2 g.), and methylene dichloride (5 g.) and the whole refluxed for 1½ hours. The hot reaction mixture was then centrifuged, and from the separated supernatant layer the *bisthio-methane* crystallised on cooling. It melted at 144—146° when recrystallised from ethanol (Found: C, 61·4; H, 5·7; N, 7·9; S, 17·4. $C_{19}H_{22}O_2N_2S_2$ requires C, 61·0; H, 5·9; N, 7·5; S, 17·1%).

Bis-p-acetamidomethylphenylsulphonylmethane (IV; R_1 = CH_2·NHAc, R_2 = R_3 = H).—Oxidation of the above bisthio-methane (0·75 g.) in acetic acid (5 ml.) with 60% hydrogen peroxide (1·5 ml.) in the usual way gave the *disulphone* which, recrystallised from 60% aqueous acetic acid, melted at 236—239° (Found: C, 52·0; H, 5·0; N, 5·9. $C_{19}H_{22}O_6N_2S_2$ requires C, 52·1; H, 5·0; N, 6·4%).

Bis-p-aminomethylphenylsulphonylmethane Dihydrochloride (IV; R_1 = CH_2·NH_2, R_2 = R_3 = H).—Hydrolysis of the above acetyl derivative (0·5 g.) with 2*N*-hydrochloric acid (15 ml.) for 4 hours gave the *dihydrochloride* which, recrystallised from dilute hydrochloric acid, gave white needles which did not melt at 400° but sublimed (Found: C, 42·6; H, 5·0; N, 6·4; Cl, 17·1. $C_{15}H_{18}O_4N_2S_2,2HCl$ requires C, 42·2; H, 4·7; N, 6·6; Cl, 16·6%).

p-*Benzamidomethylbenzenesulphonyl Chloride*.—*N*-Benzylbenzamide (100 g.) was gradually added to chlorosulphonic acid (300 ml.) at 15° with stirring. The temperature was then raised to 45° and kept at this level for 1 hour. The reaction mixture was worked up as described for *p*-succinimidomethylbenzenesulphonyl chloride, to give the *sulphonyl chloride*, m. p. 183—184° (after recrystallisation from chloroform–light petroleum) (Found: N, 4·7; Cl, 11·9. $C_{14}H_{12}O_3NSCl$ requires N, 4·5; Cl, 11·3%).

p-*Benzamidomethylthiophenol*.—Reduction of the above sulphonyl chloride (17 g.) with zinc (25 g.) and concentrated hydrochloric acid (55 ml.) (cf. above) yielded the *thiol*, m. p. 134—138° (after recrystallisation from alcohol) (Found: N, 6·0. $C_{14}H_{13}ONS$ requires N, 5·8%).

Bis-p-benzamidomethylphenylthiomethane (III; R_1 = CH_2·NHBz, R_2 = R_3 = H).—The above thiol (12·15 g.) and methylene dichloride (4·2 g.) were condensed in methanol (70 ml.) in which sodium (1·09 g.) had been dissolved. The *bisthio-methane*, recrystallised from acetic acid, had m. p. 163—165° (Found: N, 5·6. $C_{29}H_{26}O_2N_2S_2$ requires N, 5·6%).

Bis-p-benzamidomethylphenylsulphonylmethane (IV; R_1 = CH_2·NHBz, R_2 = R_3 = H).—The above bisthio-methane (1·25 g.) was oxidised with 60% hydrogen peroxide (2 ml.) in glacial acetic acid (15 ml.), a very large amount of acetic acid being necessary to keep the material in solution. The *product*, which is sparingly soluble in acetic acid, melted at 233—235° (Found: N, 5·0. $C_{29}H_{26}O_6N_2S_2$ requires N, 5·0%).

p-Succinimidomethylbenzenesulphonyl Chloride.—To chlorosulphonic acid (140 ml.), succinbenzylimide (14 g.) was added in portions, with stirring, at <10°. The reaction mixture was then heated to 60° for ½ hour and poured on ice. The gummy mass was stirred with two lots of ice-cold water, whereupon it crystallised. Recrystallised from chloroform–light petroleum, it melted at 153—157° (38%) (Found: Cl, 12·8. $C_{11}H_{10}O_4NCl$ requires Cl, 12·4%).

p-Succinimidomethylthiophenol.—To the above sulphonyl chloride (6·5 g.) in a mixture of alcohol (12 ml.) and water (7 ml.) were added zinc dust (11 g.) and concentrated hydrochloric acid (20 ml.) during 1 hour with continuous stirring. The reaction mixture was then heated for 2 minutes to 90°. It was then filtered and the filtrate poured into a mixture of ice-water (200 ml.) and concentrated hydrochloric acid (10 ml.). The precipitate was filtered off and dissolved in chloroform (50 ml.), and the chloroform solution washed with water, dried, and evaporated. The residue, recrystallised from alcohol, yielded the pure *thiol* as lemon-yellow crystals, m. p. 119° (68%) (Found: C, 60·0; H, 5·1. $C_{11}H_{11}NS$ requires C, 59·7; H, 5·0%).

Bis-p-succinimidomethylphenylthiomethane (III; R_1 = succinimidomethyl, R_2 = R_3 = H).—A mixture of the above thiol (1·1 g.), paraformaldehyde (0·15 g.), and chloroform (15 ml.) was saturated with hydrogen chloride. After 1 day, the reaction mixture was poured into water and the chloroform distilled off. The *bisthio-methane* which separated from the aqueous layer was recrystallised from acetic acid and had m. p. 212—216° (Found: C, 60·3; H, 4·9; N, 6·4. $C_{23}H_{22}O_4N_2S_2$ requires C, 60·8; H, 4·8; N, 6·2%).

Bis-p-succinimidomethylphenylsulphonylmethane (IV; R_1 = succinimidomethyl, R_2 = R_3 = H).—(*a*) The above bisthio-methane (0·6 g.) was oxidised in glacial acetic acid (40 ml.), in which it is sparingly soluble, with 60% hydrogen peroxide (16 ml.) as described in preceding experiments. The *disulphone* was recrystallised from a large volume of acetic acid and obtained as a white powder, m. p. 295—298° (Found: C, 53·6; H, 4·6; N, 5·3. $C_{23}H_{22}O_8N_2S_2$ requires C, 53·3; H, 4·2; N, 5·4%).

(*b*) When the bisthio-methane (7 g.) was heated with 2N-sodium hydroxide (50 ml.), it dissolved with formation of the succinyl derivative. A 3% aqueous potassium permanganate solution (9 g. of permanganate) was then added with vigorous stirring while carbon dioxide was passed through the mixture. The whole was filtered, and the filtrate decolorised with sulphur dioxide and acidified, a precipitate separating which, recrystallised from acetic acid, melted at 188—190°. On refluxing of this substance with 2N-hydrochloric acid, the succinimido-derivative, m. p. 295—298°, identical with that prepared by method (*a*), was formed.

Hydrolysis of bis-*p*-succinylaminomethylphenylsulphonylmethane (1·3 g.), m. p. 188—190°, as obtained above, by refluxing with a solution of potassium hydroxide (4 g.) in water (20 ml.) for 4 hours yielded bis-*p*-aminomethylphenylsulphonylmethane, the constitution of which was established by acetylating it to give the previously described diacetyl derivative (IV; R_1 = CH_2·NHAc, R_2 = R_3 = H), m. p. 236—239°.

RESEARCH DEPARTMENT, ROCHE PRODUCTS LTD.,
WELWYN GARDEN CITY, HERTS.

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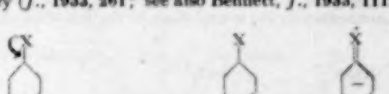
129. *A Connection between the Size of an Atom and the Magnitude of its Mesomeric and Electromeric Effects.*

By G. BADDELEY.

The ability of a covalently bonded atom to donate electrons is shown to be a function of the direction of the electron displacement. Atoms with a covalent-bond radius which is small relative to the atomic radius are shown to be sterically the most suitable for participation in double-bond formation.

THE mesomeric electron release by halogen, which was first represented by a curved arrow as in (I) * and subsequently interpreted as a resonance hybrid of canonical structures as in (II) *, has been assumed to increase in the order F < Cl < Br < I (Ingold, *Rec. Trav. chim.*, **1929**, **48**, 797). This order, which was later supported by the mesomeric moments of the halogenobenzenes (Sutton, *Proc. Roy. Soc.*, **1931**, *A*, **133**, 668), was soon recognised to be inconsonant with the effect of nuclear attached halogen on the reactivities of aromatic side chains (Shoesmith and Slater, *J.*, **1926**, 214; Ingold, *Ann. Reports*, **1927**, 156). The chemical data were collated by Bennett and Baddeley (*J.*, **1933**, 261; see also Bennett, *J.*, **1933**, 1112) and led these authors



(I.) (II.)

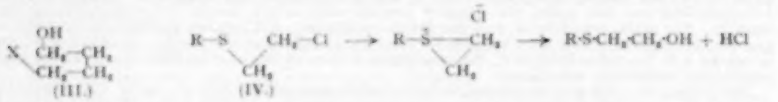
to conclude that the mesomeric and electromeric release of electrons by halogen decreases in the order F > Cl > Br > I. Branch, Yabroff, and Bettmann (*J. Amer. Chem. Soc.*, **1934**, **56**,

* In this paper double bonds are not shown in benzene rings.

1868) reached the same conclusion independently in the following year. This reversed order, which was subsequently confirmed by accurate determinations of mesomeric moments by Groves and Sugden (*J.*, **1937**, **1992**) and by Audsley and Goss (*J.*, **1942**, **497**), has been further substantiated by Bennett and others. Recently the data have been summarised and augmented by Baker and Hopkins (*J.*, **1949**, **1089**).

The original and very plausible assumption (Ingold, *loc. cit.*) that the mesomeric and electromeric release of electrons increases in the sequence F < Cl < Br < I derived, at least indirectly, from the decrease in the ionisation potential in passing from the smaller to the larger halogen atoms. There is ample evidence, however, that the ability of an atom to participate in double-bond formation by releasing electrons in the direction of an atom to which it is already covalently attached is not directly related to its ability to release electrons in other directions. This is clearly illustrated by the following comparison of the contributions made by sulphur and oxygen respectively to the properties of some organic compounds containing one or both of these elements.

When a thioether RSR′ forms a sulphonium salt $RR'R''\overset{+}{S}\,\overset{-}{X}$, the direction of the release of electrons by the sulphur atom makes an angle of approximately 110° with the bonds joining this atom to R and R′ and occurs far more readily than the corresponding release of electrons by the oxygen atom of the ether ROR′. Bennett and Mosses (*J.*, **1931**, **2956**) suggested that the interaction of the δ-hydroxy-sulphide (III; X = SPh) with hydrobromic acid is greatly facilitated by the sulphur atom which " allows one of its lone pairs of electrons to take part in



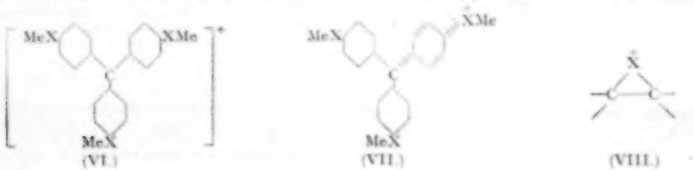
the process whereby the hydroxyl group becomes separated from the carbon atom to which it is attached." This type of activation is apparent, but in much smaller degree, for both the glycol (III; X = OH) and the phenoxy-alcohol (III; X = OPh) (Bennett and Reynolds, *J.*, **1935**, **131**).

The ready unimolecular hydrolysis of 2-chloroethyl sulphides (IV) is a consequence of a release of electrons by sulphur to the 2-carbon atom (Bennett and Baddeley, *loc. cit.*; Baddeley, Thesis, Sheffield, 1932). This electron displacement makes an angle of approximately 60° with the bond joining the sulphur atom to the 1-carbon atom and is not apparent in the rates of hydrolysis of the corresponding 2-chloro-ethers (Böhme and Sell, *Ber.*, **1948**, **81**, 123). Fehnel and Carmack (*J. Amer. Chem. Soc.*, **1949**, **71**, 84) have shown that the optical interaction of a sulphur atom with a vinyl, carbonyl, or carbalkoxyl group is not destroyed when a methylene group is interposed; this release of electrons to a " β-carbon atom " becomes negligible in each instance when the sulphur atom is replaced by oxygen.

On the other hand, oxygen has a greater tendency than has sulphur to adopt the onium state by double-bond formation: $R'-\overset{+}{X}-R \longrightarrow R'-\overset{+}{X}=\overset{-}{R}$ (X = O or S). The very ready hydrolysis of α-chloro-ethers and -thio-ethers (V; X = O and S respectively) is probably due to an electron displacement of this type (Hughes and Ingold, *J.*, **1935**, **248**), and the chloro-ethers are the more reactive (Böhme, *Ber.*, **1941**, **74**, **248**; see also Leimu and Salomaa, *Acta Chem. Scandinavica*, **1947**, **1**, **353**).

(V.) $R{\cdot}\overset{+}{X}{\cdot}CH_2\overset{-}{Cl} \longrightarrow$ Products of hydrolysis

The *pp′p″*-trimethoxytriphenylcarbonium ion (VI; X = O) is more stable than the *pp′p″*-trismethylthiotriphenylcarbonium ion (VI; X = S) (Brand, *J. pr. Chem.*, **1925**, **109**, **36**). Thus quinonoid structures of type (VII), in which electron release by X results in double-bond formation, make a greater contribution to the actual state of the ion when X = O than when X = S.



This reversal is further illustrated by the data in the table below (Bennett and Hafez, *J.*, 1941, 652). An *ortho*-substituent in 2-phenylethyl alcohol is suitably placed to donate electrons directly to the hydroxymethylene group, and the *o*-methylthio-group provides a much faster reaction with hydrobromic acid than does the *o*-methoxyl group. On the other hand, the methoxyl group is the more effective in the *p*-position; here the release of electrons is into the benzene ring and results in double bonding.

Velocities of reaction of substituted alcohols $C_6H_4X\cdot CH_2\cdot CH_2\cdot OH$ *with hydrobromic acid at* 80°: $k \times 10^6$.

X =	NO_2.	H.	I.	SMe.	OMe.
p-	1·65	5·90	6·9	11·0	106
o-	3·10	5·90	3·25	6,840	35·0

Briefly, *the oxygen atom releases electrons more readily in the direction of its covalent bonds than does the sulphur atom, whereas the latter provides the readier release of electrons in other directions. This reversal is also observed among the halogens.*

The reactivities of *cyclo*hexanol derivatives towards hydrohalogen acids and the rates of acetolysis of *cyclo*hexyl *p*-bromobenzenesulphonates provide evidence of an electron release by *trans*-2-halogen and a readiness to form cyclic intermediates of type (VIII; X = halogen) which decreases in the order I > Br > Cl (Winstein, Grunwald, *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 816, 821). On the other hand, the magnitude of the mesomeric effect of halogen when attached to a benzene ring is directly related to the ability of halogen to release electrons in the direction of the C_6H_5–halogen bond and, as mentioned at the outset, decreases in the order F > Cl > Br > I. Data given by Brockway (*J. Physical Chem.*, 1937, **41**, 747) for the carbon–halogen bond lengths in the halogenomethanes has led Pauling ("Nature of the Chemical Bond," Cornell, 1940, p. 236) to deduce "that chlorine has about one-half the power to form double bonds that fluorine has."

Although it is generally recognised that the ability to form double bonds decreases from the elements of the first row to those of the second and lower rows of the Periodic Table, no wholly satisfactory explanation has yet been found. The following simple consideration indicates that atoms with a covalent-bond radius which is small in comparison with the atomic radius are sterically the most suitable for double-bond formation. A double bond comprises a σ bond and a π bond, the latter resulting from the overlap of a *p*-orbital of one atom with a *p*-orbital of the other. These *p*-orbitals are directed perpendicularly to the σ bond and their ability to overlap one another must be directly related to the extent to which each atom contacts the flank of the other. Double bonding is therefore more likely between atoms which bite deeply into one another; that is, between atoms with a single-bond radius (r) which is small in comparison with the packing radius (R). Pauling (*op. cit.*, p. 192) has related these two radii by equation (i), whereas Rees (*J. Chem. Physics*, 1948, **16**, 995) prefers equation (ii). Rewritten as equations (iii) and (iv) respectively, they show that the quotient R/r decreases as the size of the atom increases.

(i) $R = r + 0{\cdot}8$ Å. (iii) $R/r = 1 + 0{\cdot}8/(R - 0{\cdot}8)$

(ii) $R^3 = r^3 + 1{\cdot}22^3$ (iv) $R/r = [1 + 1{\cdot}22^3/(R^3 - 1{\cdot}22^3)]^{\frac{1}{3}}$

The quotient R/r for several elements is computed in the accompanying table. The necessary data have, with one exception, been extracted from Rees's paper, and parentheses indicate that R is obtained by substituting for r in equation (ii). The quotient decreases in the order F > Cl > Br > I and O > S, as does the ability of these atoms to form double bonds.

	Element.	r.	R.	R/r.		Element.	r.	R.	R/r.
1st Period	H	0·37	1·25	3·38	2nd Period	Cl	0·995	(1·56)	1·58
	F	0·64 *	(1·38)	2·15		S	1·04	(1·60)	1·54
	O	0·735	1·39	1·90		P	1·10	(1·64)	1·49
	N	0·73	(1·42)	1·94		Si	1·16	(1·68)	1·45
	C	0·77	(1·43)	1·87					
	B	0·89	(1·51)	1·70	3rd Period	Br	1·14	1·65	1·44
						Se	1·16	1·73	1·49
					4th Period	I	1·33	1·77	1·33
						Te	1·37	1·87	1·26

* Pauling, *op. cit.*, p. 179.

The contributions made by each of the canonical structures A–X and $A^{-}{=}X^{+}$ to the actual state of the molecule AX is determined by the difference in energy between these two structures.

The energy, Q, absorbed in passing from A–X to $\bar{A}=\overset{+}{X}$ comprises three terms: $Q = I - E - D$, where I and E are respectively the ionisation potential of X and the electron affinity of A in A–X, and D is the heat of dissociation of the π bond :

$$A\text{–}X \xrightarrow{I} A\text{–}\overset{+}{X} + e \xrightarrow{-E} \bar{A}\text{–}\overset{+}{X} \xrightarrow{-D} \bar{A}=\overset{+}{X}$$

When X represents the elements of one group of the Periodic Table, *e.g.*, the halogens, both I and D decrease in magnitude in passing from the smaller to the larger atoms, and the observed order F > Cl > Br > I for the mesomeric release of electrons indicates that D is more susceptible than is I to variation with change of element. On the other hand, atoms of elements in the same period of the Table have approximately the same size and the mesomeric release of electrons decreases, *e.g.*, N > O > F, as the ionisation potential increases.

The author expresses his indebtedness to Professor G. M. Bennett, C.B., F.R.S., for his valuable advice and criticism.

COLLEGE OF TECHNOLOGY, MANCHESTER. [*Received, November 26th*, 1949.]

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130. *The Autoxidation of* iso*Propylbenzene.**

By G. P. ARMSTRONG, R. H. HALL, and D. C. QUIN.

A new technique has been used for the autoxidation of *iso*propylbenzene to give αα-dimethylbenzyl hydroperoxide. An alkaline (pH 8·5—10·5) oil-in-water emulsion of the hydrocarbon absorbs oxygen at 85° to give a good yield of the hydroperoxide identical with that previously reported by Hock and Lang (*Ber.*, 1944, **77**, 257). The characteristics of the autoxidation are consistent with a radical-chain mechanism.

THE autoxidation of *iso*propylbenzene to the hydroperoxide has been described by Hock and Lang (*Ber.*, 1944, **77**, 257), who oxidised the dry purified hydrocarbon at 85° while irradiating it with ultra-violet light.

$$C_6H_5\cdot CHMe_2 + O_2 \longrightarrow C_6H_5\cdot CMe_2\cdot O\cdot OH$$

The sodium salt of the hydroperoxide was precipitated from the product by treatment with 25% aqueous sodium hydroxide; the free hydroperoxide was liberated from the salt by careful treatment with the calculated amount of mineral acid, and further purified by distillation *in vacuo*. The overall yield of hydroperoxide was 90% based on the oxygen consumed, but the rate of oxidation was slow, only 0·2 g.-mol. of oxygen being absorbed by 3 g.-mols. of *iso*propylbenzene in 24 hours.

In 1945 when the present work was commenced, the only other reported work on the uncatalysed liquid-phase autoxidation of *iso*propylbenzene was that of Stephens (*J. Amer. Chem. Soc.*, 1926, **48**, 2920), who treated *iso*propylbenzene with oxygen in dim diffused light for 3—5 weeks at 80—104°, and obtained acetophenone and formic acid in low yields, as well as a little unidentified oil. He did not report the occurrence of peroxides in his products but observed that the presence of water favoured the oxidation slightly, whereas with toluene and ethylbenzene water inhibited oxidation.

After the work described below had been completed, the Hercules Powder Co. (U.S.P. 2,438,125) described the autoxidation of *iso*propylbenzene with air or oxygen at low temperatures in the presence of dilute alkali and activated carbon. The products contained peroxides which were not isolated but were subsequently destroyed by hot sodium hydroxide solution.

Several reports describe the metal-catalysed autoxidation of *iso*propylbenzene, the earliest being D.R.P. 522,255 (I.G. Farbenind. A.-G.; *Zentr.*, 1931, I, 3721). Acetophenone and phenyldimethylcarbinol were identified among the products. Similar results were obtained by the Monsanto Chemical Co. (U.S.P. 2,447,400) who used oxygen in the presence of calcium hydroxide.

We found the rate of absorption of oxygen by an alkaline oil-in-water emulsion of *iso*propylbenzene at 85° to be much more rapid than that reported by Hock and Lang (*loc. cit.*), and obtained considerably higher concentrations of hydroperoxide in the products. The hydroperoxide was isolated from the oxidised hydrocarbon layer by fractional distillation *in vacuo*, or by precipitation of the hydrated sodium salt with 25% w/w sodium hydroxide solution and

* This paper is covered by B.P. 610,293 and pending applications.

subsequent regeneration of the free hydroperoxide with carbon dioxide. Contrary to the implied observation of Hock and Lang precipitation of the sodium salt with a slight excess of sodium hydroxide was only about 50% complete, several treatments with fresh batches of alkali being necessary to complete the precipitation. Similarly several extractions with an excess of dilute (8%) sodium hydroxide were necessary for complete extraction of the hydroperoxide into aqueous solution. This behaviour is typical of a very weak acid.

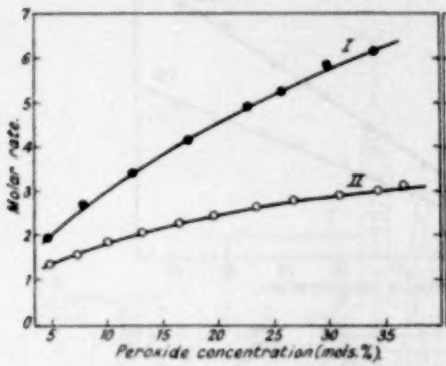
The structure of the hydroperoxide was confirmed by decomposition of the pure hydroperoxide with aqueous (10% w/v) sulphuric acid under reflux to give phenol (70—80%) and

$$C_6H_5{\cdot}CMe_2{\cdot}O{\cdot}OH \longrightarrow C_6H_5{\cdot}OH + Me_2CO$$

acetone (70%) (cf. Hock and Lang, *loc. cit.*). Small amounts of acetophenone and α-methylstyrene were obtained as by-products. It is of interest that this decomposition can be carried out equally well with the hydroperoxide in the untreated oxidation product.

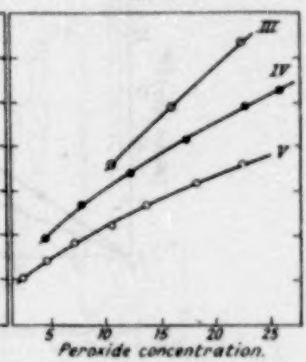
Reduction of the hydroperoxide with aqueous sodium hydrogen sulphite gave phenyldimethylcarbinol, some α-methylstyrene being formed by dehydration of the carbinol; and traces of acetophenone were again obtained.

FIG. 1.



I. 0·3% *Sodium stearate.* II. 0·4% *Teepol.*

FIG. 2.



III. *Phase ratio* 5 : 1. IV. *Phase ratio* 2 : 1. V. *Phase ratio* 1 : 1.

Preliminary work on the oxidation indicated that acids were produced in small quantities which lowered the pH of the emulsion sufficiently to slow down the oxidation. The initial presence of sodium carbonate (1·3% of the aqueous phase) provided a sufficient reserve of alkalinity without producing too high a pH in the initial stages. The presence, in the *iso*propylbenzene, of styrene and α-methylstyrene also retarded the oxidation and increased the rate of acid formation. Satisfactory starting material was obtained by hydrogenation of the crude hydrocarbon and careful fractionation of the product.

Under neutral (pH 7·4) or acid (pH 4·7) conditions, or at alkaline pH in the absence of emulsifying agent, the rate of oxidation was slow, being of the same order as the rate in the homogeneous phase at the same temperature. At high alkalinity (5—10% NaOH), the reaction efficiency (based on oxygen absorbed and hydroperoxide produced) was low, being of the order of 50%. The optimum conditions of alkalinity for a high efficiency at a reasonable rate were pH 8·5—10·5, conveniently achieved by the addition of sodium carbonate.

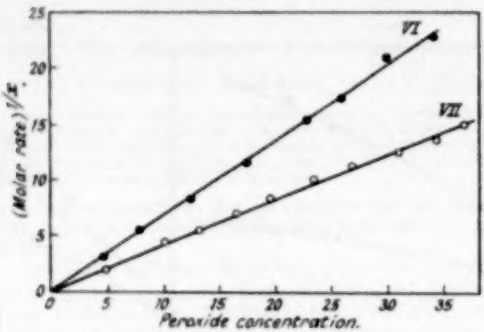
Two emulsifying agents were tried, sodium stearate and "Teepol" (an aqueous solution of mixed sodium higher-alkyl sulphates). Variation of the sodium stearate concentration between 0·09 and 0·35% w/v or of that of "Teepol" between 0·2 and 2·5% v/v in the aqueous phase did not significantly change the respective oxidation rates. However, the rate at any given hydroperoxide concentration was higher in the case of sodium stearate (Fig. 1).

The molar rate of oxidation, expressed as mols. of oxygen absorbed per hour per 100 mols. of *iso*propylbenzene present, increased with increasing water : oil phase ratio (Fig. 2), although the oxygen absorption rate per unit volume of total liquid decreased.

In the early stages of the reaction the yield of hydroperoxide based on oxygen absorbed was almost quantitative, but at 20% hydroperoxide concentration it had fallen to about 90%. The reaction was very sensitive to traces of metallic impurities, the addition of copper or lead, even as the metals, producing an immediate effect; a sharp initial rise in the rate of oxidation was followed by a rapid decline to a low value. The oxidation efficiency also fell rapidly, and the products contained up to 1 part of acetophenone for every 2 parts of hydroperoxide.

The oxidations followed a course analogous to other free-radical-chain autoxidations, for example, those of tetralin (Robertson and Waters, *Trans. Faraday Soc.*, 1946, **42**, 201) and ethyl linoleate (Bolland, *Proc. Roy. Soc., B*, 1946, **186**, 218). In the absence of added catalysts an induction period of about 1·5 hours, during which the oxygen absorption was almost imperceptible, was followed by an autocatalytic reaction. Subsequently the oxidation rate passed through a maximum value. The induction period could be eliminated by the addition of organic peroxides (benzoyl, lauryl) or of the hydroperoxide itself. Phenol inhibited the oxidation, and styrene and α-methylstyrene exerted a retarding influence (see above).

FIG. 3.



	k.	x.
VI. 0·3% *Sodium stearate*	0·80	0·58
VII. 0·4% *Teepol*	0·69	0·42

The molar rate of oxygen absorption in the autocatalytic reaction depended on the hydroperoxide concentration according to the relation

$$\text{Molar rate} = \frac{-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t}{[\mathrm{RH}]} = k[\mathrm{RO\text{-}OH}]^x$$

For a unimolecular rate of hydroperoxide decomposition the value of x expected on theoretical grounds would be 0·5 (Bolland and Gee, *Trans. Faraday Soc.*, 1946, **42**, 241). The values found approximated to this figure (Fig. 3), but with some variation. In particular the use of " Teepol " as emulsifying agent led to values of x below 0·5. A full investigation of the kinetics of the autoxidation of *iso*propylbenzene in both emulsion and single phase has been made (Twigg *et al.*, unpublished work).

The relation given above was valid up to a certain hydroperoxide concentration, which varied from one experiment to another, the highest found being 34 molar-%. Soon after this the rate passed through its maximum value. The hydroperoxide concentration continued to increase after the maximum rate had been passed, and in some cases also passed through a maximum. Where the maximum rate was observed at 34 molar-% of hydroperoxide, the concentration of the latter increased to 47 molar-% without having reached a maximum value. In other cases maximum values of both rate and hydroperoxide concentration were reached at lower extents of oxidation.

EXPERIMENTAL.

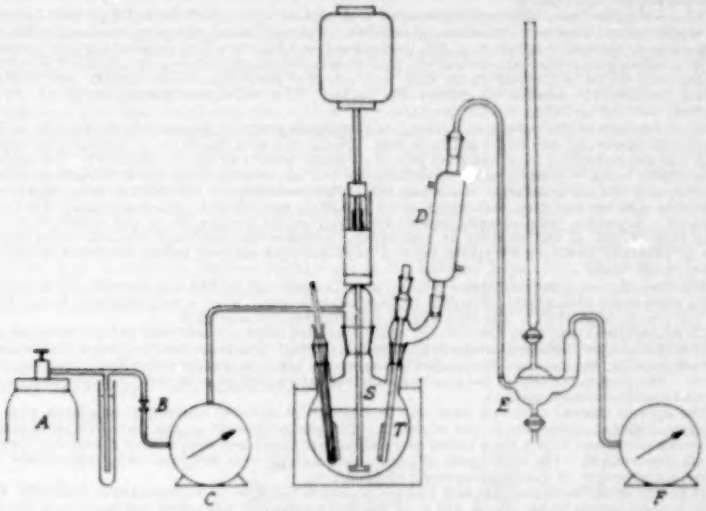
M. p.s and b. p.s are uncorrected.

Oxidation Apparatus (Fig. 4).—The oxygen feed from the supply cylinder *A* was controlled by a valve *B* operating at constant up-stream pressure, and passed *via* a ½-L. wet gasmeter *C* to the vapour space above

the liquid in the reaction vessel (a 1-l. Pyrex flask). The gas in the reaction vessel was circulated continuously through the liquid by a recycle stirrer *S*, before passing via the reflux condenser *D* and a bubbler *E* to a second gasmeter *F*. The bubbler contained aqueous phenolphthalein and was fitted with a burette for the addition of 0·2*N*-sodium hydroxide, as a rough indication of the carbon dioxide evolved. The reaction vessel was immersed in a thermostatically controlled bath, and was fitted with a thermometer pocket and a liquid-sampling tube *T*, to which were sealed glass strips to act as baffles and prevent swirling of the liquid. The seal on the stirrer shaft was filled with mercury or liquid paraffin.

Materials.—Oxygen was obtained in about 98% purity from standard commercial cylinders. *iso*Propylbenzene was received as a commercial grade containing 1—5% of styrene + α-methylstyrene. The crude material was hydrogenated for 2 hours at 60—80° and atmospheric pressure with 5% of Raney nickel as catalyst, and the hydrogenated product fractionated to give, as main fraction, *iso*propylbenzene, b. p. 153·5—154°/753 mm., n_D^{20} 1·4911, containing less than 0·005% of styrene (by ultra-violet absorption). The other materials used were of "AnalaR" grade, or in the case of sodium stearate the purest obtainable (British Drug Houses, Ltd.; made from purified stearin). "Teepol" was the commercial product supplied by Shell Chemicals Ltd.

FIG. 4.



Analytical.—*iso*Propylbenzene was examined for styrenes by ultra-violet absorption by Mr. A. R. Philpotts of this Department, whom we thank. The oxidation products were analysed for hydroperoxide as follows: Samples (1 ml.) of emulsion were pipetted into 250-ml. conical flasks each containing 25 ml. of freshly redistilled glacial acetic acid. The air in each flask was displaced by nitrogen (from cylinders; "oxygen-free" grade), and 1 ml. of saturated aqueous potassium iodide added. The flasks were stoppered and set aside for 15 minutes at room temperature, after which the liberated iodine was titrated with 0·05*N*-thiosulphate. Blank determinations on the acetic acid required about 0·1 ml. of 0·05*N*-thiosulphate.

Oxidation Procedure.—The thermostat was brought to the required temperature (normally 85°), and the air in the reaction vessel replaced by oxygen. The alkaline aqueous phase containing the emulsifying agent was introduced and allowed to reach the bath temperature. *iso*Propylbenzene was then added and the stirrer and gas circulation were started. Samples were withdrawn periodically for hydroperoxide analysis, and regular readings taken of the gasmeters.

Recovery of the Hydroperoxide.—The oxidation product was cooled to room temperature, saturated with carbon dioxide, the oil layer separated, and its hydroperoxide content determined. Subsequent treatment of the oil layer was by one of the following methods:

(*a*) The oil was cooled below room temperature, stirred, and treated dropwise with a slight excess (calculated on the oxygen absorption) of cold 25% w/w aqueous sodium hydroxide. The white crystals which separated were collected, washed with light petroleum (b. p. 40—60°), and dried in a vacuum. The *iso*propylbenzene mother-liquors still contained hydroperoxide, most of which was recovered as sodium salt by successive treatments with strong alkali as outlined above.

The sodium salt was converted into free hydroperoxide, if desired, as follows. A suspension of the salt in water was covered with light petroleum and saturated with carbon dioxide. The upper layer was separated, washed with a little water, dried (Na_2SO_4), and evaporated *in vacuo*. Distillation of the

residual free hydroperoxide at low pressure gave a colourless oil, b. p. 53°/0·0005 mm. (pump pressure), n_D^{20} 1·5242, d_4^{20} 1·062 (Found: C, 71·4; H, 8·05; active O, 10·5. Calc. for $C_9H_{12}O_2$: C, 71·05; H, 7·95; active O, 10·5%) (Hock and Lang, *loc. cit.*, give b. p. 53°/0·1 mm., 60°/0·2 mm., n_D^{20} 1·52424, d_4^{20} 1·06189). MR_D^{20} was 43·86 (Calc. for *iso*propylbenzene: 40·16); the increment for the ·O·O· group was thus 3·70.

(*b*) The oil was distilled *in vacuo*. The unchanged *iso*propylbenzene was recovered first, at 41—46°/13 mm. It contained traces of α-methylstyrene (identified by its ultra-violet absorption) and acetophenone (identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic specimen 242—244°). When all the low-boiling material had been removed, a residue of hydroperoxide remained which was distilled *in vacuo*.

Acid Decomposition of the Hydroperoxide (cf. Hock and Lang, *loc. cit.*).—(*a*) A mixture of the sodium salt (2 g.) of the hydroperoxide and 10% w/w sulphuric acid (25 c.c.) was refluxed for 1½ hours, the top of the reflux condenser being connected to a tube dipping into ice-cold water. A very slow current of water at 50—60° was passed through the condenser. When the heating was stopped the liquid in the trap connected to the top of the condenser was treated with a solution of 2 : 4-dinitrophenylhydrazine in 5*N*-hydrochloric acid. The yellow flocculent precipitate which separated was recrystallised from 95% ethanol; it formed yellow needles, m. p. 126—127°, undepressed on admixture with authentic acetone 2 : 4-dinitrophenylhydrazone.

The acid hydrolysate obtained was treated with sodium hydroxide pellets (3·5 g.) and filtered, and the filtrate benzoylated at 0° with benzoyl chloride. The solid which separated was recrystallised from 95% ethanol, whereafter it had m. p. 67°, undepressed on admixture with authentic phenyl benzoate.

In a subsequent similar experiment the hydrolysate was steam-distilled, the distillate acidified and treated with excess of bromine water, then with excess of potassium iodide solution, and finally with sodium thiosulphate solution to remove free iodine. 2 : 4 : 6-Tribromophenol, m. p. 93—94°, was obtained (lit., 92° to 96°).

(*b*) A mixture of the sodium salt (50 g.) of *iso*propylbenzene hydroperoxide (equivalent to 25·5 g. of free hydroperoxide) and dilute sulphuric acid (560 c.c. of water and 3·5 c.c. of concentrated sulphuric acid) was steam-distilled until free from phenol (bromine water test on the distillate). The main bulk of distillate, which contained some water-insoluble oil, was treated with excess of sodium hydroxide solution, and the aqueous layer was separated. The remaining oil was washed with dilute sodium hydroxide solution and then with water, dried (Na_2SO_4), and filtered. A colourless oil (4·5 c.c.) was obtained. A portion gave acetophenone 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p.). The main bulk of the oil was distilled at atmospheric pressure, the following fractions being obtained: (i) b. p. 160—165° (0·9 c.c.), n_D^{20} 1·5370, (ii) b. p. 165—210° (2·8 c.c.), n_D^{20} 1·5325, and (iii) b. p. 240—250° (0·5 c.c.), n_D^{20} 1·5467.

Fraction (i) was α-methylstyrene (lit., b. p. 162—164°, n_D^{20} 1·5384), its identity being confirmed by its ultra-violet absorption. Fraction (ii) was refractionated, more α-methylstyrene being obtained (2·1 c.c.; b. p. 160—173°). The high-boiling material was not identified.

(*c*) A mixture of sulphuric acid (17 c.c. of concentrated sulphuric acid and 270 c.c. of water) and a solution (175 c.c.) of *iso*propylbenzene hydroperoxide (65·6 g.) in *iso*propylbenzene was stirred vigorously and refluxed for 90 minutes. Steam-distillation of the mixture yielded a distillate consisting of two layers. The acetone content of the aqueous layer was determined by oximation, and the phenol content by the bromide–bromate method.

The acetone content of the oil layer was determined by repeated washing of an aliquot with water and determination of acetone in the washings. The phenol content of the layer was determined by extracting an aliquot with a large excess of *N*-sodium hydroxide and determining the phenol content of the alkaline extract. The total yields of phenol and acetone were 82% and 74%, respectively, based on the initial weight of *iso*propylbenzene hydroperoxide.

Reduction of the Hydroperoxide with Sodium Hydrogen Sulphite.—The hydrated sodium salt (830 g.) of the hydroperoxide (equiv. to *ca.* 410 g. of free hydroperoxide) was added gradually to a vigorously stirred aqueous solution (2·4 l.) of sodium hydrogen sulphite (480 g.) which was kept at <20°, the resultant mixture stirred for a further 45 minutes at room temperature, and the oil extracted with ether. The ethereal solution was washed with dilute sodium hydroxide solution and then with water, and dried (Na_2SO_4), and the ether distilled off, to yield an oil (295 g.) which was fractionated *in vacuo* through a 30 × 1·5-cm. helices-packed, jacketed, glass column. α-Methylstyrene (38 g.) was collected, mainly at 51·5—52·5°/12 mm., and, after a small intermediate fraction, phenyldimethylcarbinol (246 g.) distilled at 90—92°/11 mm. This material (n_D^{20} 1·5210) contained traces of acetophenone from which it cannot readily be separated by distillation (cf. Klages, *Ber.*, 1902, **35**, 2637). When kept, it yielded large, transparent, colourless crystals, m. p. 25—27°, which on recrystallisation from light petroleum (b. p. 40—60°), cooled in ethanol–solid carbon dioxide, yielded small white crystals, m. p. 34—35° (Matsubara and Perkin, *J.*, 1905, 671, give m. p. *ca.* 35—37°). The carbinol on dehydration with boiling acetic anhydride (Staudinger and Breusch, *Ber.*, 1929, **62**, 449) gave α-methylstyrene, b. p. 50—50·5°/11 mm., n_D^{20} 1·5384, in good yield.

The authors are indebted to the Directors of the Distillers Company, Ltd., for permission to publish this paper. The microanalysis was by Drs. Weiler and Strauss of Oxford.

The Distillers Company Limited,
Research and Development Department,
Epsom, Surrey.

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131. *Deoxy-sugars. Part IX. Some Properties and Reactions of 2-Deoxy-D-galactose.*

By W. G. Overend, F. Shafizadeh, and M. Stacey.

2-Deoxy-D-galactose, conveniently synthesised by the glycal method, gives an interesting series of highly crystalline derivatives. The reactions and general properties of the oxidation product are closely similar to those described for other 2-deoxy-hexoses and -pentoses. The synthesis and determination of the structure of the methyl-glycopyranosides and -glycofuranosides of 2-deoxy-D-galactose are described.

We have extended our studies of deoxy-sugars, and in particular of 2-deoxy-pentoses and -hexoses to include 2-deoxy-D-galactose; the preparation of this compound was reported by Isbell and Pigman (*J. Res. Nat. Bur. Stand.*, **1939**, **22**, 397) but not its derivatives or reactions. We found that 2-deoxy-D-galactose could be synthesised in satisfactory yield from D-galactose by the improved glycal method. We noted that the Zemplén method for the deacetylation of 3 : 4 : 6-triacetyl D-galactal gave a better yield than that employing barium hydroxide as the deacetylating agent. Treatment of D-galactal with 5% sulphuric acid gave 2-deoxy-D-galactose. We observed that catalytic reduction of 3 : 4 : 6-triacetyl D-galactal yielded 3 : 4 : 6-*triacetyl* 1 : 2-*dideoxy*-D-*galactose*, deacetylation of which, using sodium in methanol, afforded 1 : 2-*dideoxy*-D-*galactose*, which was also obtained by catalytic reduction of D-galactal. Further investigations of these interesting dideoxy-sugars will form the subject of a later communication.

2-Deoxy-D-galactose exhibited mutarotation in water and in methanol. It formed a crystalline 2 : 4-*dinitrophenylhydrazone* and when treated with *p*-toluidine in ethanol gave 2-*deoxy*-D-*galactose* p-*toluidide*. Both derivatives are particularly useful for characterising the sugar. On acetylation with acetic anhydride in pyridine, 2-deoxy-D-galactose was converted into 1 : 3 : 4 : 6-*tetra-acetyl* 2-*deoxy*-α-D-*galactose*, whereas when fused sodium acetate and acetic anhydride were used as acetylating agents the β-isomer of the *tetra-acetate* was obtained. It was shown that 2-deoxy-D-galactose could react in its *aldehydo*-form, since when treated with ethanethiol and concentrated hydrochloric acid it gave crystalline 2-*deoxy*-D-*galactose diethyl mercaptal*. Oxidation of the deoxy-sugar with bromine in water was easily effected, the product being 2-*deoxy*-D-*galactonolactone*. Treatment of this lactone with liquid ammonia gave the corresponding *amide* which on being heated evolved ammonia. 2-Deoxy-D-galactonolactone was extremely stable and underwent no apparent hydrolysis in aqueous solution in 3 days, indicating that it was probably a furanolactone.

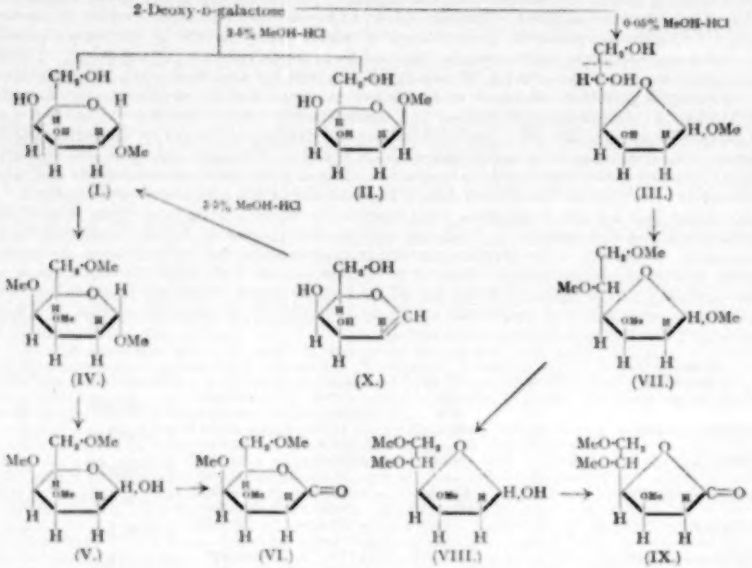
Methyl glycopyranosides of	Isomer.	M. p.	$[\alpha]_D$.	$[M]$.	$[M]_\alpha - [M]_\beta$	Ref.
L-Arabinose	α	131°	+ 17·3°	2,840	−37,420	*a*
	β	169	+245·5	40,260		
2-Deoxy-L-ribose	α	99—100	− 43·4	− 6,420	−36,360	*b*
	β	83—84	+202·3	29,940		
D-Glucose	α	168	+158·9	30,830	+37,030	*c*, *d*
	β	110	− 31·97	− 6,200		
2-Deoxy-D-glucose	α	91—92	+138	+24,600	+33,180	*e*, *f*
	β	122—123	− 48·2	− 8,500		
D-Galactose	α	111	+178·8	33,300	+33,380	*g*, *h*
	β	178	− 0·42	−80·5		
2-Deoxy-D-galactose	α	112—113	+170	+30,300	+30,300	
	β	Syrup	± 0	0		

a, Hudson, *J. Amer. Chem. Soc.*, 1925, **47**, 270. *b*, Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836. *c*, Rüber, *Ber.*, 1924, **57**, 1797. *d*, Patterson and Robertson, *J.*, 1929, 300. *e*, Bergmann *et al.*, *Ber.*, 1922, **55**, 158. *f*, *Idem*, *ibid.*, 1920, **53**, 545. *g*, Fischer and Beensch, *ibid.*, 1894, **27**, 2480; 1895, **28**, 1145; Voss, *Annalen*, 1931, **485**, 283; Michael and Littman, *ibid.*, 1928, **466**, 115. *h*, Müller, *Ber.*, 1931, **64**, 1820.

When 2-deoxy-D-galactose was treated with 2·5% methanolic hydrogen chloride for three hours it yielded a syrup from which was isolated a crystalline methyl-2-deoxygalactoside. This, as is subsequently described, was identified as α-methyl-2-deoxy-D-galactopyranoside (I) which was conveniently characterised by conversion into its 3 : 4 : 6-*tritoluene*-p-*sulphonyl* derivative. In addition to (I) a syrupy glycoside was obtained which in all probability consisted mainly of β-*methyl*-2-*deoxy*-D-*galactopyranoside* (II). Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1630) described the isolation of similar compounds but did not investigate their structures. Polarimetric observations on the specific rotations, in methanol, of the two glycosides served to differentiate between the α- and β-isomers in accordance with the well-known convention, first

introduced by Hudson (*J. Amer. Chem. Soc.*, 1909, **31**, 66) (cf. Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836). Moreover the αβ-relation of the two isomeric glycosides was further confirmed by the observations which were made (polarimetrically) that 2% methanolic hydrogen chloride converts each glycoside into an αβ-mixture similar to that from which they were initially isolated (Fig. 1). Finally the αβ-relation between the two glycosides is evident from a consideration of the difference in molecular rotations. The molecular rotations of the α- and β-forms ($[M]_\alpha$ and $[M]_\beta$ respectively) of the methylglycopyranosides of L-arabinose, 2-deoxy-L-ribose, D-glucose, 2-deoxy-D-glucose, D-galactose, and 2-deoxy-D-galactose are compared in the annexed table (cf. Deriaz *et al.*, *loc. cit.*). There is good agreement between the difference in the molecular rotations of the respective α- and β-forms of methyl-2-deoxy-D-galactopyranoside and of methyl-D-galactoside.

When 2-deoxy-D-galactose was treated with 0·05% methanolic hydrogen chloride for a very short period, another methyl-2-deoxy-D-galactoside (III) was formed. This has been shown to be αβ-*methyl-2-deoxy-D-galactofuranoside* (cf. Deriaz *et al.*, *loc. cit.*, and Hughes, Overend, and Stacey, *J.*, 1949, 2846, for analogous results with 2-deoxy-D-ribose and 2-deoxy-D-glucose respectively).



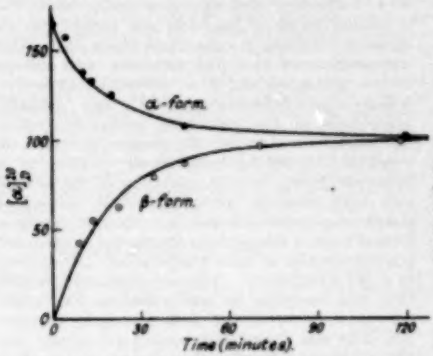
The following observed facts have led to the glycosides (I) and (III) being assigned the structures described.

(*a*) The glycoside (III) was much more rapidly hydrolysed with hydrochloric acid than glycoside (I). In Fig. 2 the rates of hydrolysis of the glycosides (I) and (III) and of αβ-methyl-D-galacto-pyranoside and -furanoside are compared. It is a general property of methylglyco-furanosides to have a greater lability to acids than the corresponding pyranosides and this effect is enhanced in the series of 2-deoxy-sugars (Overend, Stacey, and Staněk, *J.*, 1949, 2841). This result indicates that the glycosides (I) and (III) are of the pyranose and furanose type respectively.

(*b*) When D-galactal (X) was treated with 3·3% methanolic hydrogen chloride it yielded the crystalline glycoside (I) (33%). Since D-galactal is known to have the pyranose structure (Levene and Tipson, *J. Biol. Chem.*, 1931, **93**, 631) it is likely that (I) also has a pyranose structure (cf. Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509, for a similar approach in the glucose series).

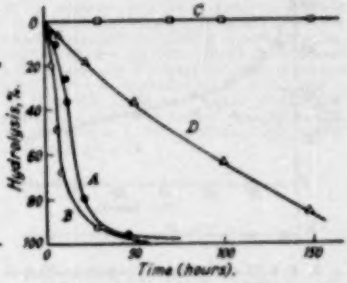
(*c*) It is well established (Hockett and McClenahan, *J. Amer. Chem. Soc.*, **1939**, **61**, 1667) that adjacent hydroxyl groups are readily oxidised by lead tetra-acetate and that *cis*- are more rapidly oxidised than *trans*-hydroxyl groups. Oxidation of the glycosides (I) and (III) with lead tetra-acetate resulted in both cases in the uptake of 1 mole of oxidant. The rate of oxidation was slightly faster for (I) than for (III) (see Fig. 3). Similarly adjacent hydroxyl groups may be oxidised by sodium metaperiodate (Jackson and Hudson, *J. Amer. Chem. Soc.*, **1939**, **61**, 1530).

FIG. 1.



Isomerisation of α- and β-methyl-2-deoxy-D-galactopyranoside by 2·5% HCl in MeOH.

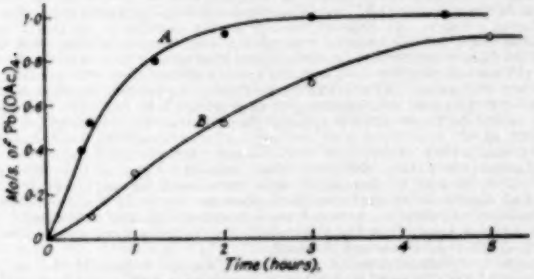
FIG. 2.



A. αβ-Methyl-2-deoxy-D-galactofuranoside (0·02N-HCl).
B. α-Methyl-2-deoxy-D-galactopyranoside (N-HCl).
C. αβ-Methyl-D-galactopyranoside (0·5N-HCl).
D. αβ-Methyl-D-galactofuranoside (N-HCl).

FIG. 3.

Oxidation by lead tetra-acetate.



A. α-Methyl-2-deoxy-D-galactopyranoside.
B. αβ-Methyl-2-deoxy-D-galactofuranoside.

If one of the hydroxyl groups is primary then formaldehyde is formed. Both glycosides absorbed 1 mole of sodium metaperiodate, but formaldehyde resulted only from (III), thereby indicating that this glycoside was methyl-2-deoxy-D-galactofuranoside. The formaldehyde was determined as its dimedon derivative (Reeves, *J. Amer. Chem. Soc.*, **1941**, **63**, 1476).

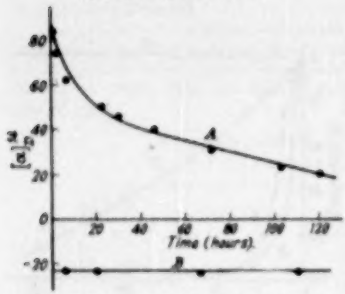
(*d*) Finally, conclusive proof of the structures of the glycosides was obtained by the classical methods of carbohydrate chemistry, involving methylation of the glycoside, hydrolysis of the fully methylated derivative, oxidation of the products to methylated lactones, study of the rates

of hydrolysis of the methylated lactones in water, etc. (Carter, Robinson, and Haworth, *J.*, 1930, 2125).

Thus α-methyl-2-deoxy-D-galactopyranoside (I) was methylated by the liquid ammonia technique (Muskat, *J. Amer. Chem. Soc.*, 1934, **56**, 693, 2449; Freudenberg and Boppel, *Ber.*, 1938, **71**, 2505). Smooth methylation occurred and **3 : 4 : 6-*trimethyl* α-*methyl*-2-*deoxy*-D-*galactopyranoside*** (IV) was obtained as a colourless liquid. On treatment with N-hydrochloric acid at 70° it gave **3 : 4 : 6-*trimethyl* 2-*deoxy*-D-*galactopyranose*** (V) as a colourless syrup. Oxidation of this with bromine in water afforded **3 : 4 : 6-*trimethyl* 2-*deoxy*-D-*galactonolactone*** (VI). A similar series of reactions was carried out on αβ-methyl-2-deoxy-D-galactofuranoside (III). This was methylated in liquid ammonia with sodium and methyl iodide and **3 : 5 : 6-*trimethyl* αβ-*methyl*-2-*deoxy*-D-*galactofuranoside*** (VII) was isolated. Hydrolysis of the glycosidic group by 0·01N-hydrochloric acid at 100° (20 minutes) gave **3 : 5 : 6-*trimethyl* 2-*deoxy*-D-*galactofuranose*** (VIII) as a colourless syrup, whence oxidation in the normal way with bromine water gave **3 : 5 : 6-*trimethyl* 2-*deoxy*-D-*galacionolactone*** (IX). The rate of hydrolysis of each of the lactones obtained was measured polarimetrically at room temperature. Hydrolysis of **3 : 4 : 6**-trimethyl 2-deoxy-D-galactonolactone (VI) was complete in approximately 100 hours, whereas **3 : 5 : 6**-trimethyl 2-deoxy-D-galactonolactone (IX) was hydrolysed exceedingly slowly (see Fig. 4), thereby showing that the original methylglycosides from which they were derived must have had the pyranose (I) and the furanose structure (III) respectively.

FIG. 4.

Hydrolysis of the lactones.



A. **3 : 4 : 6-*Trimethyl* 2-*deoxy*-D-*galactonolactone*** (δ-*type*).

B. **3 : 5 : 6-*Trimethyl* 2-*deoxy*-D-*galactonolactone*** (γ-*type*).

Thus it was apparent that the above reactions of 2-deoxy-D-galactose are closely analogous to those of 2-deoxy-D-ribose and 2-deoxy-D-glucose, and it seems that these will be typical for most 2-deoxy-hexoses and -pentoses.

EXPERIMENTAL.

3 : 4 : 6-*Triacetyl* D-*Galactal*.—Dry powdered 1-bromo 2 : 3 : 4 : 6-tetra-acetyl D-galactose (110 g.) was suspended in 50% acetic acid (1·6 l.), and the suspension was rapidly stirred. Zinc dust (300 g.) was slowly added during 2 hours. At intervals throughout the addition of the zinc a few drops of a 3% solution of platinic chloride were added. Stirring was continued for 3 hours and then the zinc was filtered off, and the filtrate concentrated to 500 c.c. and then poured into water (1 l.). The solution was extracted with chloroform (4 × 250 c.c.), and the extract washed first with aqueous sodium hydrogen carbonate and then with water. After being dried ($MgSO_4$) the solvent was evaporated and the syrupy residue distilled. Two fractions were obtained, (i) 48 g. (69%), b. p. 145—150° (bath temp.)/0·001 mm., n_D^{18} 1·4677, m. p. *ca.* 30°, $[\alpha]_D^{18}$ ±0° (*c*, 1·0 in ethanol) {this was triacetyl D-galactal (cf. Levene and Tipson, *J. Biol. Chem.*, 1931, **93**, 631, who give m. p. 30° and $[\alpha]_D$ −12·4° in chloroform, and Komada, *Bull. Jap. Chem. Soc.*, 1932, **7**, 211, who gives b. p. 138—140°/0·2—0·3 mm.; Pigman and Isbell, *J. Res. Nat. Bur. Stand.*, 1937, **19**, 204, who record b. p. 140—155°/0·005 mm.)}, and (ii) 1·1 g., b. p. 180—210° (bath temp.)/0·001 mm. (Found: C, 50·9; H, 6·3%). Trituration of (ii) with ethanol induced a portion to crystallise. This was separated and shown to be penta-acetyl D-galactose, m. p. 142° alone or on admixture with an authentic specimen. In addition some polymeric material remained undistilled. If the addition of platinic chloride solution was omitted the yield of triacetyl D-galactal was much reduced (*ca.* 30%) and much more penta-acetyl D-galactose was obtained.

3 : 4 : 6-*Triacetyl* 1 : 2-*Dideoxy*-D-*galactose*.—**3 : 4 : 6**-Triacetyl D-galactal (0·5 g.) was dissolved in dry methanol (50 c.c.) and hydrogenated at room temperature with a platinum oxide catalyst. The solution was filtered and evaporated to dryness. The syrupy residue was distilled and **3 : 4 : 6-*triacetyl* 1 : 2-*dideoxy*-D-*galactose*** (0·45 g.) obtained as a colourless syrup, b. p. 120—130° (bath temp.)/1 mm., n_D^{18} 1·4558, $[\alpha]_D^{18}$ +55·9° (*c*, 0·32 in chloroform) (Found: C, 52·5; H, 6·8. $C_{12}H_{18}O_7$ requires C, 52·5; H, 6·6%).

D-*Galactal*.—(*a*) **3 : 4 : 6**-Triacetyl D-galactal (32 g.) was added to a solution of barium hydroxide (90 g.) in water (450 c.c.). The solution was kept overnight at 0° and then heated for 30 minutes at 80°. Carbon dioxide was passed through the solution after cooling and the precipitated barium carbonate filtered off. The filtrate was evaporated at 55° to half its volume and then refiltered through a charcoal pad. Further evaporation gave crystals which were recrystallised from ethyl acetate. D-Galactal (10 g., 59%) had m. p. 104° and $[\alpha]_D^{18}$ +3° (*c*, 1·2 in methanol) (cf. Levene and Tipson, *loc. cit.*, and Komada *loc. cit.*, who give m. p. 100°, and Tamm and Reichstein, *Helv. Chim. Acta*, 1948, **31**, 1630, who give m. p. 90—92°).

(*b*) 3 : 4 : 6-Triacetyl D-galactal (87 g.) was dissolved in absolute methanol (1 l.), and sodium (0·2 g.) was added. The solution was kept for 48 hours and then solid carbon dioxide was added. The solution was evaporated to dryness, the residue was recrystallised from ethyl acetate, and D-galactal (38 g., 81%), m. p. 104°, was obtained.

1 : 2-*Dideoxy*-D-*galactose*.—(*a*) D-Galactal (0·5 g.) was dissolved in methanol (25 c.c.) and hydrogenated at room temperature with a Raney nickel catalyst. After cessation of the uptake of hydrogen the catalyst was filtered off and the filtrate was evaporated to dryness. The syrupy residue crystallised from aqueous ethanol in plates. 1 : 2-*Dideoxy*-D-*galactose* (0·4 g.) had m. p. 128—129° and $[\alpha]_D^{20}$ +41·8° (*c*, 0·526 in water) (Found: C, 48·7; H, 7·9. $C_6H_{12}O_4$ requires C, 48·6; H, 8·1%). (*b*) 3 : 4 : 6-Triacetyl 1 : 2-dideoxy-D-galactose (1·0 g.) was dissolved in dry methanol (15 c.c.) and sodium (15 mg.) was added. The solution was kept at room temperature for 48 hours and then evaporated to dryness. The residue was extracted with a small amount of ethanol, and the solvent was re-evaporated. Repeated recrystallisation of the product from ethanol afforded 1 : 2-dideoxy-D-galactose identical with the product above. Reacetylation of 1 : 2-dideoxy-D-galactose (1 g.) with acetic anhydride (5 c.c.) in pyridine (10 c.c.) regenerated 3 : 4 : 6-triacetyl 1 : 2-dideoxy-D-galactose, b. p. 120—125° (bath temp.)/1 mm., n_D^{15} 1·4560.

2-*Deoxy*-D-*galactose*.—D-Galactal (6·1 g.) was dissolved in 5% sulphuric acid (85 c.c.) and the solution was kept at 0° for 24 hours. Then the solution was warmed to 60° and neutralised with barium carbonate which was added portionwise. The solution was filtered and decolorised by stirring it with charcoal. It was concentrated under reduced pressure to a syrup which was taken up in methanol (3 vols.) and set aside. 2-Deoxy-D-galactose (4·5 g.) crystallised from solution and was recrystallised from methanol as colourless needles (3·4 g.) which had m. p. 110° and $[\alpha]_D^{20}$ +57° → +2° (equilibrium) (*c*, 1·0 in water) (Found: C, 43·9; H, 7·1. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3%) [cf. Isbell and Pigman, *J. Res. Nat. Bur. Stand.*, 1939, **22**, 397, who give m. p. 120—121° and $[\alpha]_D$ +40·8° → +60·5° (equilibrium in 30 minutes; *c*, 4·0 in water); Tamm and Reichstein, *loc. cit.*, who give m. p. 105—106° and $[\alpha]_D^{18}$ +60·7° in water]. 2-Deoxy-D-galactose exhibited mutarotation in several solvents:

(*a*) Methanol as solvent (*c*, 0·58):

Time, mins.	1·5	2·5	5·5	9·5	11·0
$[\alpha]_D^{17}$	.....	+3·44°	+17·25°	+32·2°	+32·2°	+32·2°

(*b*) Water as solvent (*c*, 1·19):

Time, mins.	2	3	4·5	7	13	18	30	40	46	50
$[\alpha]_D^{17}$	.....	+33·6°	+35·2°	+37°	+38·6°	+46·2°	+50·2°	+54·5°	+56·2°	+57°	+57°

2-*Deoxy*-D-*galactose* 2 : 4-*Dinitrophenylhydrazone*.—2-Deoxy-D-galactose (0·3 g.) in water (10 c.c.) was added to a solution of 2 : 4-dinitrophenylhydrazine (0·7 g.) in glacial acetic acid (10 c.c.), and the mixture was warmed at 90° for 30 minutes. The solvents were then removed under diminished pressure and the residue was crystallised by trituration with ethanol. Recrystallisation from aqueous ethanol gave 2-*deoxy*-D-*galactose* 2 : 4-*dinitrophenylhydrazone*, m. p. 124°, and $[\alpha]_D^{20}$ +30° in methanol (Found: C, 41·5; H, 4·9. $C_{12}H_{14}O_5N_4$ requires C, 41·8; H, 4·7%).

2-*Deoxy*-D-*galactose* p-*Tolusidide* [with A. B. Foster].—2-Deoxy-D-galactose (0·3 g.) dissolved in ethanol (7 c.c.; 95%) was added to *p*-tolusidine (0·23 g., 1·1 mols.), and the solution boiled under reflux for 2 hours. When kept overnight at room temperature the product separated in large prisms. Recrystallisation from ethanol gave 2-*deoxy*-D-*galactose* p-*tolusidide* (0·25 g.; 54%) as white prisms, m. p. 142—143°, $[\alpha]_D^{20}$ −149° (*c*, 0·8 in pyridine) (Found: C, 61·9; H, 7·6; N, 5·2. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·5; N, 5·5%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2-*Deoxy*-α-D-*galactose*.—2-Deoxy-D-galactose (0·41 g.) was added to a mixture of freshly distilled acetic anhydride (2·0 g.) in dry pyridine (10 c.c.). The mixture was kept for 2 days and then poured into water. The turbid solution was extracted with chloroform, and the extract washed with dilute sulphuric acid and then water. After being dried ($MgSO_4$) the solvent was evaporated and the residue was distilled. 1 : 3 : 4 : 6-*Tetra-acetyl* 2-*deoxy*-α-D-*galactose* (0·4 g.) was obtained as a thick colourless syrup, b. p. 160—170°/0·01 mm., n_D^{20} 1·4618, $[\alpha]_D^{20}$ +67° in methanol (Found: C, 51·1; H, 6·3. $C_{14}H_{20}O_8$ requires C, 50·6; H, 6·1%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2-*Deoxy*-β-D-*galactose*.—2-Deoxy-D-galactose (0·41 g.), freshly fused and powdered sodium acetate (0·5 g.), and redistilled acetic anhydride (7 c.c.) were heated together under reflux for 30 minutes. The resulting solution was then poured into ice-cold water (100 c.c.) which was extracted with chloroform. The extract was washed with dilute aqueous sodium hydrogen carbonate and with water. After drying ($MgSO_4$) the solvent was removed by evaporation and the residue distilled. 1 : 3 : 4 : 6-*Tetra-acetyl* 2-*deoxy*-β-D-*galactose* (0·5 g.) was obtained as a thick colourless syrup, b. p. 195° (bath temp.)/0·001 mm., n_D^{20} 1·4580, $[\alpha]_D^{20}$ +46·6° in methanol (Found: C, 51·0; H, 6·1%).

2-*Deoxy*-D-*galactose Diethyl Mercaptal*.—Finely divided 2-deoxy-D-galactose (0·5 g.) was added to concentrated hydrochloric acid (0·5 c.c.) at 0°. Ethanethiol (1 c.c.) was added and the mixture was shaken for 4 hours. Water was added and the insoluble material collected. Crystallisation from aqueous ethanol gave 2-*deoxy*-D-*galactose diethyl mercaptal* (0·27 g.), m. p. 107—108°, $[\alpha]_D^{20}$ +40° (*c*, 0·25 in methanol) (Found: C, 44·7; H, 8·0; S, 23·4. $C_{10}H_{22}O_4S_2$ requires C, 44·4; H, 8·2; S, 23·6%).

2-*Deoxy*-D-*galactonolactone*.—2-Deoxy-D-galactose (2·59 g.) was dissolved in water (25 c.c.), and bromine (5 c.c.) was added. The mixture was kept at 37° for 1 day or at room temperature for 1 week. After these periods the solution no longer reduced Fehling's solution. The excess of bromine was removed by aeration and the hydrogen bromide by precipitation with silver carbonate. Silver in solution was removed by treatment with hydrogen sulphide. After filtration through charcoal the solution was evaporated to dryness and the residue triturated with absolute methanol. Crystallisation from dry acetone gave beautiful crystals of 2-*deoxy*-D-*galactonolactone* (1·4 g.), m. p. 97—98°, $[\alpha]_D^{20}$ −12·1° in water (Found: C, 44·4; H, 6·3. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2%). This lactone apparently underwent no hydrolysis in water in 3 days.

2-Deoxy-D-galactonamide.—2-Deoxy-D-galactonolactone (0·45 g.) was dissolved in absolute methanol (10 c.c.) in a Dewar flask. Liquid ammonia was added and the mixture was kept until all the ammonia had evaporated (48 hours). The methanol was evaporated and the syrupy residue was triturated with acetone. After recrystallisation from aqueous acetone, *2-deoxy-D-galactonamide monohydrate* (0·14 g.) was obtained as a colourless powder, m. p. (indefinite) 90—102° with decomposition and evolution of ammonia, $[\alpha]_D^{20}$ +5·3° (*c*, 0·38 in methanol) (Found: C, 36·8; H, 7·4. $C_6H_{13}O_5N,H_2O$ requires C, 36·5; H, 7·6%).

α-Methyl-2-deoxy-D-galactopyranoside.—2-Deoxy-D-galactose (10 g.) was dissolved in 2·5% methanolic hydrogen chloride (200 c.c.) and the reaction was followed polarimetrically. When reaction was complete (2 days), the solution was neutralised with silver carbonate and filtered. The filtrate was evaporated, and on addition of ethyl acetate to the residue part of it crystallised. The solid was separated and repeatedly recrystallised from ethyl acetate. α-Methyl-2-deoxy-D-galactopyranoside (4·2 g.) was obtained as colourless plates, m. p. 112—113°, $[\alpha]_D^{20}$ +169·6° ±2° (*c*, 0·38 in methanol) (Found: C, 47·2; H, 8·2; OMe, 17·8. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·8; OMe, 17·4%) [cf. Tamm and Reichstein *Helv. Chim. Acta*, 1948, **31**, 1640) who give m. p. 109—110° and $[\alpha]_D^{20}$ +171·8° ±2° in methanol]. To the syrupy product remaining after the separation of the solid α-methyl-2-deoxy-D-galactopyranoside, ethyl acetate was added, and the solution was passed through a column of activated alumina. A syrupy product was isolated, which did not reduce Fehling's solution and was presumably *β-methyl-2-deoxy-D-galactopyranoside* (4 g.), n_D^{20} 1·4869, $[\alpha]_D^{20}$ ±0° in methanol (Found: C, 47·0; H, 7·2; OMe, 17·0. $C_7H_{14}O_5$ requires C, 47·2; H, 7·8; OMe, 17·4%).

Action of Methanolic Hydrogen Chloride on D-Galactal.—D-Galactal (1·66 g.) in 3·3% methanolic hydrogen chloride (10 c.c.) was kept for 1·5 hours, and then the solution was neutralised with silver carbonate. The product was isolated in the manner described above and recrystallised repeatedly from ethyl acetate. *α-Methyl-2-deoxy-D-galactopyranoside* (0·64 g.) was obtained having m. p. 112—113°, $[\alpha]_D^{20}$ +170° (*c*, 0·32 in methanol) (Found: C, 47·2; H, 8·4%).

αβ-Methyl-2-deoxy-D-galactofuranoside.—2-Deoxy-D-galactose (2·5 g.) was dissolved in absolute methanol (60 c.c.), and 5·0% methanolic hydrogen chloride (0·6 c.c.) was added. The reaction ensuing was followed polarimetrically and was arrested at the maximum lævorotatory value by addition of silver carbonate and silver oxide. The solution was filtered through a charcoal pad and then concentrated under diminished pressure. The syrupy residue did not reduce Fehling's solution and was *αβ-methyl-2-deoxy-D-galactofuranoside*, n_D^{20} 1·4828, $[\alpha]_D^{20}$ −68° (*c*, 0·68 in methanol) (Found: C, 48·5; H, 8·3; OMe, 17·7%). Attempts to distil this compound resulted in a change which is being further investigated, but on rapid distillation a small portion did distil [b. p. 170° (bath temp.)/0·001 mm., n_D^{20} 1·4830, $[\alpha]_D^{20}$ −81·2° (*c*, 1·0 in methanol) (Found: C, 46·98; H, 7·8; OMe, 17·0. $C_7H_{14}O_5$ requires C, 47·2; H, 7·8; OMe, 17·4%)].

Treatment of α- and β-Methyl-2-deoxy-D-galactopyranoside with Methanolic Hydrogen Chloride.—(*a*) α-Methyl-2-deoxy-D-galactopyranoside was dissolved in 2% methanolic hydrogen chloride (*c*, 8·0) and the change in optical rotation was observed at intervals. The following results were noted.

Time, mins.	0	5	9	14	20	53	124
$[\alpha]_D^{20}$	+170°	160°	135°	130°	124°	110°	102°

(*b*) A similar procedure was carried out with β-methyl-2-deoxy-D-galactopyranoside. The results obtained were as follows.

Time, mins.	0	5	9	14	22	35	50	80	110
$[\alpha]_D^{20}$	±0°	+10°	47°	53°	64°	80°	90°	96°	98°

Lead Tetra-acetate Oxidations.—(a) *Pyranoside.* α-Methyl-2-deoxy-D-galactopyranoside (0·0278 g.) was dissolved in glacial acetic acid (20 c.c.), and a solution of freshly prepared lead tetra-acetate in glacial acetic acid (25 c.c. of 0·069 N.) was added. The final volume was made up to 50 c.c. with glacial acetic acid. The oxidation was followed titrimetrically by withdrawing 5-c.c. samples at intervals and estimating iodometrically the unused lead tetra-acetate.

Time, hours	0·30	0·45	1·0	1·3	2·18	3·0	4·6	5·4
Uptake of $Pb(OAc)_4$, mol. equiv.	0·40	0·58	0·64	0·82	0·92	1·03	1·15	1·15

(b) *Furanoside.* A similar procedure was carried out on αβ-methyl-2-deoxy-D-galactofuranoside (0·0289 g.), with results as follows.

Time, hours	0·5	1·0	2·0	3·0	5·0	10·0
Uptake of $Pb(OAc)_4$, mol. equiv.	0·10	0·33	0·52	0·70	0·90	1·00

Sodium Metaperiodate Oxidations.—(*a*) αβ-Methyl-2-deoxy-D-galactofuranoside (0·0234 g.) was added to N-sodium hydrogen carbonate (5 c.c.), and 0·173N-sodium metaperiodate (5 c.c.) was added. The mixture was set aside for 2 hours and then sodium arsenite (0·084N.; 15 c.c.) and N-hydrochloric acid (5 c.c.) were added. After the disappearance of the yellow colour, N-sodium acetate (5 c.c.) and a dimedon solution (2 c.c. of a solution of dimedon (0·8 g.) in ethanol (10 c.c.)] were added and the solution was heated at 100° for 10 minutes. After 1 hour the precipitate was collected and weighed after being thoroughly washed with water and dried at 90—95° for 20 minutes. The precipitate (m. p. 189—190°; cf. Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476, who reports m. p. 189—190° for this complex), corresponded in weight (0·04 g.) to the formation of 1 mole of formaldehyde. In a separate experiment it was shown that 1 mole of oxidising agent was consumed by the furanoside in 4 hours.

(*b*) When a similar procedure was carried out with α-methyl-2-deoxy-D-galactopyranoside, no precipitate was formed on addition of the dimedon reagent showing that no formaldehyde had been liberated.

3 : 4 : 6-*Tritoluene-p-sulphonyl* α-*Methyl-2-deoxy-*D*-galactopyranoside.—α-Methyl-2-deoxy-D-galactopyranoside (0·185 g.) was added to a solution of toluene-*p*-sulphonyl chloride (3·3 mols., 0·7 g.) in dry pyridine (7 c.c.). After being kept for 2 days the solution was poured into ice-water and the precipitate collected. Crystallisation from methanol gave **3 : 4 : 6-*tritoluene*-p-*sulphonyl* α-*methyl-2-deoxy-*D*-galactopyranoside** (0·25 g.), m. p. 147°, $[\alpha]_D^{20}$ +52° (*c*, 0·076 in methanol) (Found: C, 53·1; H, 4·8. $C_{28}H_{32}O_{11}S_3$ requires C, 52·4; H, 5·0%).

3 : 4 : 6-*Trimethyl* α-*Methyl-2-deoxy-*D*-galactopyranoside.—α-Methyl-2-deoxy-D-galactopyranoside (2·8 g.) was added to liquid ammonia (200 c.c.), and sodium (1·5 g.) was added in small pieces. After 20 minutes methyl iodide (15 c.c.) was added. When the liquid ammonia had evaporated, anhydrous magnesium sulphate was added to the residue which was extracted with ether (1 l.). The solvent was evaporated and the syrupy residue was methylated twice more by the same procedure. The crude product obtained was distilled and **3 : 4 : 6-*trimethyl* α-*methyl-2-deoxy-*D*-galactopyranoside** (0·96 g.) was obtained as a colourless mobile liquid, b. p. 95—105° (bath temp.)/0·001 mm., n_D^{20} 1·4445, $[\alpha]_D^{20}$ +138·5° in methanol (Found: C, 54·5; H, 9·2; OMe, 56·7. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·1; OMe, 56·3%).

3 : 4 : 6-*Trimethyl* 2-*Deoxy-*D*-galactopyranose.—The fully methylated glycoside (2·8 g.) and N-hydrochloric acid (25 c.c.) were heated together at 70° for 5 hours and at 90° for 1 hour. The hydrolysis was followed polarimetrically and was complete after this time. The solution was neutralised with silver carbonate, filtered, and evaporated. Ethanol was added to the residue which was re-evaporated after filtering. After similar treatment with ether the residue was distilled and **3 : 4 : 6-*trimethyl* 2-*deoxy-*D-*galactopyranose** (0·518 g.) obtained as a clear colourless viscous liquid, b. p. 150—160° (bath temp.)/0·001 mm., n_D^{20} 1·4637, $[\alpha]_D^{20}$ +41° in methanol (Found: C, 52·2; H, 8·2; OMe, 43·4. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

3 : 4 : 6-*Trimethyl* 2-*Deoxy-*D*-galactonolactone (*δ-Type*).—**3 : 4 : 6**-Trimethyl 2-deoxy-D-galactopyranose (0·36 g.) in aqueous solution (15 c.c.) and bromine (3 c.c.) were kept at 37° for 3 days. The excess of bromine was removed by aeration, and hydrogen bromide by silver oxide. Passage of hydrogen sulphide removed silver ions in solution. After filtration the solution was evaporated to dryness and the residue distilled. **3 : 4 : 6-*Trimethyl* 2-*deoxy-*D-*galactonolactone*** was obtained as a colourless liquid, b. p. 154—161° (bath temp.)/0·001 mm., $[\alpha]_D^{20}$ +81·7° in water (Found: C, 52·3; H, 8·0; OMe, 45·6. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9; OMe, 45·1%). Polarimetric observations indicated that in aqueous solution (*c*, 1·125) it was hydrolysed in 4 days.

Time, hours	0	1	6	22	30	47	72	103	130
$[\alpha]_D^{20}$	+82°	75°	63°	51°	46°	41°	32°	22°	22°

3 : 5 : 6-*Trimethyl* αβ-*Methyl-2-deoxy-*D*-galactofuranoside.—αβ-Methyl-2-deoxy-D-galactofuranoside (1·6 g.) was added to liquid ammonia (200 c.c.), and then sodium (1·2 g.) was added. After 20 minutes methyl iodide (8 c.c.) was added. The product was isolated as already described and was methylated twice more. **3 : 5 : 6-*Trimethyl* αβ-*methyl-2-deoxy-*D*-galactofuranoside** (0·64 g.) was obtained as a pale straw-coloured liquid, b. p. 130—135° (bath temp.)/12 mm., n_D^{20} 1·4421, $[\alpha]_D^{20}$ −29·7° in water (Found: C, 54·3; H, 9·4; OMe, 54·7. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·1; OMe, 56·3%).

3 : 5 : 6-*Trimethyl* 2-*Deoxy-*D*-galactofuranose.—**3 : 5 : 6**-Trimethyl αβ-methyl-2-deoxy-D-galactofuranoside (0·47 g.) and 0·01N-hydrochloric acid (45 c.c.) were heated together under reflux for 20 minutes. After neutralisation (Ag_2CO_3) and filtration the solution was concentrated under diminished pressure. Addition of ethanol served to remove colloidal silver. After filtration, benzene was added and the solution concentrated. Distillation of the residue gave **3 : 5 : 6-*trimethyl* 2-*deoxy-*D-*galactofuranose** (0·375 g.) as a clear, thick syrup, which strongly reduced Fehling's solution, m. p. 105—110° (bath temp.)/0·001 mm., n_D^{20} 1·4535, $[\alpha]_D^{20}$ −35·1° (*c*, 2·05 in methanol), $[\alpha]_D^{20}$ −24° (*c*, 1·0 in water; mutarotation complete in 7 minutes) (Found: C, 52·5; H, 8·8; OMe, 46·0. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

3 : 5 : 6-*Trimethyl* 2-*Deoxy-*D*-galactonolactone (*γ-Type*).—**3 : 5 : 6**-Trimethyl 2-deoxy-D-galactofuranose (0·15 g.) in water (5 c.c.) was treated with bromine (1 c.c.) for 2 weeks. The product was isolated in the usual manner, and **3 : 5 : 6-*trimethyl* 2-*deoxy-*D-*galactonolactone*** (46 mg.) was obtained as a colourless liquid, b. p. 140—151° (bath temp.)/0·001 mm., n_D^{20} 1·4520 (Found: C, 52·2; H, 8·2; OMe, 43·8. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9; OMe, 45·1%).

Polarimetric observations on an aqueous solution of this lactone indicated that no detectable hydrolysis occurred in over 100 hours.

Time, hours	0·5	4·5	21·5	68·75	93·75	110
$[\alpha]_D^{20}$	−24·9°	−24·9°	−25°	−25·6°	−25°	−25·8°

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THE CHEMISTRY DEPARTMENT,
THE UNIVERSITY, BIRMINGHAM.

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132. 1 : 2 : 5 : 6-*Tetrahydropyridine: Isolation from Technical Piperidine by Efficient Fractional Distillation.*

By W. H. Davies and L. L. McGee.

Technical piperidine has been fractionally distilled and found to contain some water, about 20% of 1 : 2 : 5 : 6-tetrahydropyridine, b. p. 117·4°/771 mm., and only 70% of piperidine, b. p. 106°. The unsaturated base was identified by a series of derivatives. Traces of α-picoline and tetrahydropicolines have also been found in some samples.

For over 40 years, and from different countries, there have been reports that technical piperidine, presumably prepared by reduction of pyridine, usually contains unsaturated impurities. When pure piperidine has been required, it has been obtained by making an *N*-derivative, *e.g.*, the nitroso- (Vorländer and Wallis, *Annalen*, 1906, **345**, 277) or the benzoyl (Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, *B*, 60) derivative, oxidising away the unsaturated material with permanganate in acetone, and hydrolysing off the protecting group.

Reduction of alkyl-substituted pyridines with sodium in alcohol is known to give tetrahydro-derivatives which appear to be Δ^1- or Δ^4-isomers (Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 508: Koenigs *et al.*, *Ber.*, 1905, **38**, 3042, 3928; 1907, **40**, 3199). Marie and Lejeune (*J. Chim. physique*, 1925, **22**, 59) stated that electrolytic reduction of pyridine gave piperidine in about 65% yield together with about 20% of tetrahydropyridine. The evidence for the latter was that a semi-crystalline mass separated from the distillation residue; this was assumed to be "dipiperidein," the dimer of 2 : 3 : 4 : 5-tetrahydropyridine previously obtained by Lellman and Schwaderer (*Ber.*, 1889, **22**, 1319) by the action of alkali on *N*-chloropiperidine. In a patent (Tech. Res. Works, B. P. 309,300) it is reported that hydrogenation of pyridine over nickel at 180°/300 lb. gives 80% of piperidine and about 10% of tetrahydropyridine, b. p. 93—95°. Again, no evidence was given that the product was a tetrahydropyridine; the low boiling point is surprising and suggests that this fraction may have been the piperidine–water azeotrope, b. p. 92·8° (cf. Horsley, *Ind. Eng. Chem., Anal.*, 1947, **19**, 508). Apart from this work, the compounds responsible for the unsaturation in technical piperidine have not, so far as we are aware, been isolated or characterised.

As we required pure piperidine, we examined several samples of commercially available piperidine. Material sold as 96% piperidine was slightly yellow and a "pure" sample, sold as 98—99% piperidine, was water-white; apart from this yellow impurity, the samples seemed to be identical and the "pure" was probably obtained by total distillation of the 96% material. Samples of both types were found to have b. p. 106° (by direct determination) but by good fractionation gave three main products: (i) 6%, b. p. 92° (piperidine–water azeotrope; cf. Horsley, *loc. cit.*), (ii) 70%, b. p. 106° (pure piperidine), and (iii) 20%, b. p. 117°. (These percentages are roughly corrected for the losses in the intermediate fractions.) A very small and variable amount of higher-boiling bases, mainly b. p. 123°, was also obtained in some cases. The 117° fraction was freed from traces of pipecolines (methylhexahydropyridines) by azeotropic distillation.

The infra-red absorption spectrum of the base of b. p. 117° showed that it was free from pyridine, picolines, and pipecolines. Analysis of the base itself and of its *acetyl* and *benzoyl* derivatives (from which the base could be regenerated) agreed with the empirical formula C_5H_9N, *i.e.*, a tetrahydropyridine. Hydrogenation over Raney nickel resulted in absorption of 1 mole of hydrogen to give piperidine (identified by physical constants and its benzoyl derivative).

The three tetrahydropyridines have previously been reported. The base, b. p. 117°, cannot be the 2 : 3 : 4 : 5-tetrahydro-compound because it forms *N*-acyl derivatives. The 1 : 2 : 3 : 4-tetrahydro-isomer [obtained by caustic fusion of "*N*-oxypiperidine" (Wolffenstein, *Ber.*, 1892, **25**, 2783) or piperidine-2-sulphonic acid (Paal and Hubaleck, *Ber.*, 1901, **34**, 2761)] gives an oily benzoyl derivative and a hydrochloride, m. p. 230° (decomp.); the m. p.s of the corresponding derivatives of the base, b. p. 117°, were 60—62° and 191—193° (decomp.). The 1 : 2 : 5 : 6-tetrahydropyridine has been prepared by Renshaw and Conn (*J. Amer. Chem. Soc.*, 1938, **60**, 745) by treating 4-bromopiperidine with sodium methoxide. They reported m. p.s (or decomposition points) for the hydrochloride, aurichloride, platinichloride, and *N*-methyl methiodide (*i.e.*, 1 : 1-dimethyl-1 : 2 : 5 : 6-tetrahydropyridinium iodide) in close agreement with those of the corresponding derivatives of our base, b. p. 117°, which is therefore, beyond doubt, 1 : 2 : 5 : 6-tetrahydropyridine. Renshaw and Conn did not isolate the free base because of its "ready polymerisation;" we find, on the other hand, that the free base is stable under ordinary conditions and can be distilled without appreciable polymerisation.

The amount of the higher-boiling fraction, b. p. 123°, varied with different samples of technical piperidine and was in all cases very small. Infra-red absorption spectra indicated the presence of *C*-methyl groups and unsaturation. From chemical evidence, this fraction was clearly a mixture. On conversion into its picrate, a mixture was formed from which α-picoline picrate was isolated in 17% yield. After mild hydrogenation, α-picoline was again isolated as its picrate (in 14% yield) and α-pipecoline as its *benzenesulphonyl* derivative. It is probable, therefore, that the fraction of b. p. 123° is a mixture of α-picoline (about 20%) and one or more of its tetrahydro-derivatives (about 80%), these properties being in agreement with the picoline isolated as picrate and with the hydrogen absorption.

Catalytic hydrogenation of pyridine over Raney nickel and over nickel on kieselguhr was examined but there was no appreciable formation of 1 : 2 : 5 : 6-tetrahydropyridine. Not all samples of commercially available piperidine contained the unsaturated base, and it seems possible that it is only present when the " piperidine " is manufactured by electrolytic reduction of pyridine. It is curious that the mixture in this technical piperidine should have approximately the correct b. p. for pure piperidine (106°) : presumably the water and the tetrahydropyridine balance the b. p. to give this fortuitous result.

Experimental.

Distillation of Technical Piperidine.—The following is a typical batch run. A column (14″ × ¾″) packed with ¼″ × ¼″ stainless-steel gauze rings was used : theoretical plates at total reflux, 46; at 10 c.c. per hour take-off rate, 30 (approx.); at 20 c.c. per hour take-off, 20 (approx.). Pressure, 756·5 mm. Charge : 200 c.c. of good-quality technical piperidine (sold as 95·5% piperidine).

Fraction no.	Temp.	Vol. (c.c.).	% of total.	Take-off rate (c.c./hr.).	Reflux ratio
1	92°	10	5	10	30 : 1
2	92—106	3·0	1·5	10	30 : 1
3	106	125·0	62·5	20	15 : 1
4	106—117	13·4	6·7	10	30 : 1
5	117	33·5	16·7	20	15 : 1
Residue	—	11·0	—	—	—
Column hold-up	—	5·0	—	—	—

Fraction 1 was the azeotrope of piperidine (65%) and water (cf. Horsley, *loc. cit.*). After this fraction had been dried (KOH), infra-red absorption spectra indicated that it was mainly piperidine and that it was substantially free from pipecolines (azeotrope, b. p. 92—93°). The total piperidine content (fractions 1—3) was about 70%.

Fraction 5 was 1 : 2 : 5 : 6-tetrahydropyridine, the content of which in the technical piperidine must be about 20%.

Purification of 1 : 2 : 5 : 6-*Tetrahydropyridine.*—The base (fraction 5, above; 45 c.c.) and water (10 c.c.) were distilled to give fractions : (i) b. p. 92—93° (3%), (ii) b. p. 95° (26%), and (iii) b. p. 117° (20%). At this point, a further 5 c.c. of water was added and the distillation continued to give the azeotrope of 1 : 2 : 5 : 6-tetrahydropyridine, b. p. 95°, identical with fraction (ii). The azeotrope was dried (KOH) and distilled, to give 1 : 2 : 5 : 6-*tetrahydropyridine*, b. p. 117°, m. p. −48° (Found : C, 71·85; H, 10·65; N, 16·6. C_5H_9N requires C, 72·16; H, 10·8; N, 16·8%).

Fraction (i) was shown to be an azeotrope in which pipecolines were identified by infra-red absorption. Similar results were obtained with other samples of technical piperidine.

B. p. Determinations.—Technical piperidine, 105·6°; pure piperidine, 105·6°; 85% piperidine +15% 1 : 2 : 5 : 6-tetrahydropyridine (water-free), 106·7°.

Derivatives of 1 : 2 : 5 : 6-*Tetrahydropyridine.*—*Acetyl* (by refluxing in acetic anhydride), b. p. 117°/19 mm., n_D^{25} 1·4985, m. p. *ca.* −3° (Found : N, 11·3. $C_7H_{11}ON$ requires N, 11·2%). *Benzoyl* (by Schotten–Baumann method), b. p. 113°/0·15 mm., m. p. 60—62° (from light petroleum) (Found : C, 76·7; H, 6·95; N, 7·65. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%). *Picrate*, m. p. 161—163° (from water) (Found : N, 17·7. $C_5H_9N,C_6H_3O_7N_3$ requires N, 17·9%). Hydrochloride (from ethanol), m. p. 191—193° (Found : Cl′, 29·3. Calc. for C_5H_9N,HCl : Cl′, 29·7%). Aurichloride, m. p. 141—142° (decomp.). Platinichloride, m. p. 187—188° (m. p. depends on rate of heating). Metho-methiodide, m. p. 274—275° (decomp.) (Found : I′, 53·0. Calc. for $C_5H_{11}N,CH_3I$: I′, 53·1%). For the corresponding last four derivatives of 1 : 2 : 5 : 6-tetrahydropyridine, Renshaw and Conn (*loc. cit.*) give m. p. 188—189°, 141° (decomp.), 187—188° (decomp.), and 274—275°, respectively.

Base of B. p. 123°.—This was obtained by fractionating the higher-boiling residues from a number of distillations of technical piperidine. The crude picrate, prepared in water, had m. p. 133—144° and was crystallised from water to give α-picoline picrate (17%), m. p. (alone or mixed with an authentic sample) 164—166° (Found : C, 44·7; H, 3·1; N, 17·3. Calc. for $C_6H_7N,C_6H_3O_7N_3$: C, 44·7; H, 3·1; N, 17·4%); the *benzenesulphonyl* derivative (prepared by the Schotten–Baumann method) had m. p. 67—69° (from methanol) (Found : C, 60·4; H, 6·1; N, 5·7. $C_{12}H_{15}O_2NS$ requires C, 60·8; H, 6·3; N, 5·9%). This is a derivative of a methyltetrahydropyridine but the positions of the methyl group and double bond were not established.

The base of b. p. 123° (2 g.) in dioxan (15 c.c.) was hydrogenated at ordinary temperature and pressure over platinum (0·2 g.) (Hydrogen absorption : 380 c.c. Calc. for $C_6H_{11}N$, 460 c.c. Calc. for 80% $C_6H_{11}N$, 370 c.c.). On conversion of part of the reduced base into its picrate, a mixture was obtained

from which α-picoline picrate was isolated in 14% yield. The rest of the reduced base was treated with benzenesulphonyl chloride under Schotten–Baumann conditions to give *N-benzenesulphonyl-α-pipecoline* (30%), m. p. 64—66° (from light petroleum), alone or mixed with an authentic sample (Found: C, 60·25; H, 6·75; N, 5·7. $C_{12}H_{17}O_2NS$ requires C, 60·2; H, 7·1; N, 5·9%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH LABORATORIES, HEXAGON HOUSE, BLACKLEY, MANCHESTER. [*Received, November* 10th, 1949.]

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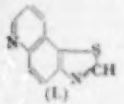
133. *Some Naphthothiazoles.*

By W. A. BOGGUST, WESLEY COCKER, J. C. P. SCHWARZ, and E. R. STUART.

Naphtho(1′ : 2′-4 : 5)thiazole and *naphtho*(2′ : 1′-4 : 5)*thiazole* have been prepared and their light-absorption characteristics compared with those of pyridino(2′ : 3′-6 : 7)benzthiazole. Attempts to prepare naphtho(2′ : 3′-4 : 5)thiazole are described.

RECENTLY Cocker and Boggust (*J.*, 1949, 355) described a new quinthiazole which was assumed to be the angular compound, pyridino(2′ : 3′-6 : 7)benzthiazole (I). Two angular naphthothiazoles have now been prepared for comparison of their light-absorption properties with those of the quinthiazole. These compounds, naphtho(1′ : 2′-4 : 5)thiazole (II) and *naphtho*(2′ : 1′-4 : 5)*thiazole* (III), were obtained by the route used by Mercury, Vincent, and Sherrill (*J. Amer. Chem. Soc.*, 1946, **68**, 1594) which involves oxidative ring closure of the appropriate naphthylthio-oxamic acid to the corresponding naphthothiazole-2-carboxylic acid which is then decarboxylated. The naphthothiazole (II) had previously been obtained by Hofmann (*Ber.*, 1887, **20**, 1798, 2265) from formo-α-naphthylamide and sulphur. The compound (III) was also obtained by an alternative method described below.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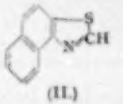
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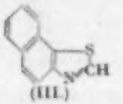
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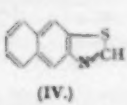
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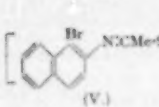
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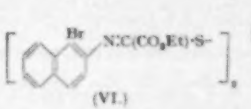
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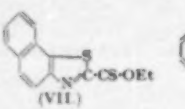
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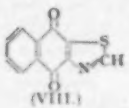
(VIII.)

All attempts to prepare naphtho(2′ : 3′-4 : 5)thiazole (IV) were unsuccessful. Attempted cyclisation of 1-*bromo*-2-*naphthylthio-oxamic acid* or its *ethyl* ester, obtained by thionation of *ethyl* 1-*bromo*-2-*naphthyloxamate* in toluene, yielded a product which on heating with mineral acid gave 1-bromo-2-naphthylamine. A similar experience was recorded by Levkoev and Baskirova (*Chem. Abstr.*, 1947, **41**, 447) who showed that 1-bromo-2-thioacetamidonaphthalene on oxidation yielded the disulphide (V), which gave 1-bromo-2-naphthylamine when heated with mineral acid. These workers also showed that the "linear naphthothiazole" of Fries and Buchler (*Annalen*, 1927, **454**, 260) prepared by oxidation of 1-bromo-2-thiobenzamidonaphthalene is, in reality, a similar disulphide. When ethyl 1-bromo-2-naphthyloxamate was thionated in boiling xylene it yielded a mixture of an unidentified, sparingly soluble compound which may be the *disulphide* (VI) and *ethyl naphtho*(2′ : 1′-4 : 5)*thiazole*-2-*thioncarboxylate* (VII) (the latter being produced with elimination of bromine). (VII) was hydrolysed to *sodium naphtho*(2′ : 1′-4 : 5)*thiazole*-2-*carboxylate*, and this gave the parent thiazole (III) when boiled with acid.

Naphtho(2′ : 3′-4 : 5)*thiazole*-1′ : 4′-*quinone* (VIII) was prepared by condensation of 2-amino-1 : 4-naphthaquinone-3-thiol with formaldehyde in weakly acid solution (cf. B.P. 262,141/1926), the resulting thiazoline being spontaneously oxidised during isolation as shown by the fact that the product is unaffected by hydrogen peroxide. All attempts to reduce the quinone to the naphthothiazole were unsuccessful.

We were unable to obtain 2-methylnaphtho(2′ : 3′-4 : 5)thiazole by the method of B.P. 445,538, as in our hands the preparation of 2-aminonaphthalene-3 : 6-disulphonyl chloride recorded there failed. Further attempted deamination of 1-bromo-2-aminonaphtho(2′ : 3′-4 : 5)thiazole (Hunter and Jones, *J.*, 1930, 941) gave unpromising results.

Ultra-violet light absorption data are as follows :

Compound :	(I).		(II).		(III).	
	$\lambda_{max.}$ A.	log ε.	$\lambda_{max.}$ A.	log ε.	$\lambda_{max.}$ A.	log ε.
	2500	4·35	2310	4·80	2300	4·35
					2500	4·60
	(2900	3·7)	2900	3·93	2800	3·75
					2900	3·73
	3320	3·31	3250	3·09	3250	2·79
					3350	2·81

The higher degree of resolution apparent in (III) is in accordance with previous experimental evidence that addition of an auxochrome or chromophore in the 2-position in naphthalene produces a more complex spectrum than does substitution in the 1-position (Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; A.P.I. Research Project 44 Nat. Bur. Stand. Catalog of U.V. Spectral Data, Serial Nos. 244—247, 1- and 2-naphthols, contributed by U.O.P. Co., Riverside, Illinois; Cocker *et al.*, to be published).

Naphtho(2′ : 3′-4 : 5)thiazole-1′ : 4′-quinone shows maxima at 2450 A. (log ε 4·45), 2800 A. (log ε 4·20), and 3400 A. (log ε 3·52), characteristic of tricyclic quinones (Spruit, *Rec. Trav. chim.*, 1949, **68**, 325).

All light-absorption measurements were made in alcoholic solution using the Beckman model DU quartz spectrophotometer.

Experimental.

(Analyses are by Drs. Weiler and Strauss.)

Naphtho(1′ : 2′-4 : 5)*thiazole* (II).—Ethyl 1-naphthyloxamate was obtained substantially as described by Ballo (*Ber.*, 1873, **6**, 247).

1-*Naphthylthio-oxamic acid.* The above oxamic ester (11 g.) in boiling anhydrous xylene (220 c.c.) was slowly treated with phosphorus pentasulphide (6·9 g.), and refluxing was continued for 1 hour. The hot xylene was decanted from some tarry material and was distilled in steam, leaving an oily residue consisting of the thio-ester, which was shaken with an excess of cold 10% sodium hydroxide solution until a clear solution was obtained. After filtration, the solution was acidified and the *thio-oxamic acid* (10 g.; m. p. 117°) was crystallised from light petroleum (b. p. 60—80°) as yellow needles, m. p. 124—125° (Found : C, 62·4; H, 4·2. $C_{12}H_9O_2NS$ requires C, 62·4; H, 3·9%).

Naphtho(1′ : 2′-4 : 5)*thiazole.* A filtered solution of the crude thio-oxamic acid (10 g.) in 10% sodium hydroxide solution (330 c.c.) was stirred and slowly treated with a solution of potassium ferricyanide (75 g.) in water (180 c.c.). The yellowish-brown precipitate which formed was collected and immediately refluxed with 8% hydrochloric acid (150 c.c.) for 1 hour. The hot solution was filtered from Prussian blue, boiled with charcoal, and filtered. On cooling, the hydrochloride of the required thiazole was obtained (5·5 g.). It readily dissociated when heated or in water, but crystallised satisfactorily from concentrated hydrochloric acid as pale yellow needles, m. p. 185°. The hydrochloride (5·0 g.), basified with aqueous ammonia, yielded the thiazole (2·9 g.) which crystallised from light petroleum (b. p. 40—60°) as large, pale yellow prisms, m. p. 53—54° (cf. Hofmann, *loc. cit.*, who gives m. p. 45—46°) (Found : C, 71·0; H, 4·0. Calc. for $C_{11}H_7NS$: C, 71·3; H, 3·8%).

Naphtho(2′ : 1′-4 : 5)*thiazole* (III).—Ethyl 2-naphthyloxamate was obtained as described by Meyer and Muller (*Ber.*, 1897, **30**, 770).

2-*Naphthylthio-oxamic acid.* This was prepared from ethyl 2-naphthyloxamate (11 g.) as described for the 1-isomer. A small sample crystallised from water as yellow, glistening plates, m. p. 269—271°, but a satisfactory analysis was not obtained.

Naphtho(2′ : 1′-4 : 5)*thiazole.* The foregoing crude thio-oxamic acid was treated as in the preparation of (II). The hydrochloride of the required thiazole was not isolated, but its clarified solution (charcoal) in 10% hydrochloric acid was basified with aqueous ammonia, and the *product* (3·4 g.; m. p. 60°) crystallised from dilute alcohol as colourless plates or needles, m. p. 65° (Found : C, 70·8; H, 3·6%).

Ethyl 1-*Bromo*-2-*naphthyloxamate.*—Ethyl 2-naphthyloxamate (24·5 g.) was brominated in the minimum quantity of cold chloroform with bromine (5·5 c.c.) in chloroform (15 c.c.). After 1 hour, the chloroform was removed in a vacuum, and the crude ester was washed with aqueous sodium carbonate and crystallised from alcohol as colourless needles (27·5 g.), m. p. 99—99° (Found : C, 52·2; H, 3·7. $C_{14}H_{12}O_3NBr$ requires C, 52·2; H, 3·7%). The compound was also obtained when 1-bromo-2-naphthylamine was refluxed for 1 hour with ethyl oxalate.

Thionation, in Xylene, of Ethyl 1-*Bromo*-2-*naphthyloxamate.*—The compound (16·6 g.) in boiling anhydrous xylene (350 c.c.) was slowly treated with phosphorus pentasulphide (11·5 g.), and refluxing was continued for 45 minutes. Hydrogen bromide was evolved, especially during the later stages of the reaction. The hot xylene was decanted and cooled, yielding a yellow solid (*A*; 4·5 g.), m. p. 100—230°. On extraction with ether, (*A*) left a residue (*B*; 3·3 g.), m. p. 250—275° (according to the rate of heating) which crystallised from xylene as red needles. After melting, it resolidified and then gave m. p. 328—331°. We were unable to identify (*B*), but it may be the *disulphide* (VI) (Found : C, 49·6; H, 2·7. $C_{28}H_{22}O_4N_2S_4Br_2$ requires C, 49·6; H, 3·3%), since it is sparingly soluble in organic solvents, *e.g.*, ethanol, ethyl acetate, and benzene, requiring boiling xylene for recrystallisation, and thus probably has a relatively high molecular weight. The mother-liquor from (*A*) was evaporated in a vacuum to 50 c.c. and cooled, whereupon yellow crystals (*C*) were deposited. The mother-liquor from (*C*) was evaporated to dryness in a vacuum, and the resulting tarry solid crystallised from dilute alcohol as yellow needles

(2·9 g.), m. p. 100—110° (according to rate of heating), consisting of *ethyl naphtho*(2′ : 1′-4 : 5)*thiazole*-2-*thiocarboxylate* (VII) (Found: C, 61·4; H, 4·1; S, 21·1. $C_{14}H_{11}ONS_2$ requires C, 61·5; H, 4·0; S, 23·4%). Extraction of (C) with ether gave a further 1 g. of the thion-ester. The ester (VII) (0·5 g.) was heated for 10 minutes with 10% aqueous sodium hydroxide (2·0 c.c.) in water (100 c.c.), and the hot solution was filtered and cooled, yielding *sodium naphtho*(2′ : 1′-4 : 5)*thiazole*-2-*carboxylate* as colourless plates, m. p. 350—355° (Found: S, 11·6. $C_{12}H_4O_2NSNa,H_2O$ requires S, 11·9%). The salt was boiled for 90 minutes with 15% hydrochloric acid, and the hot solution was filtered, cooled, and basified with aqueous ammonia, giving naphtho(2′ : 1′-4 : 5)thiazole (0·2 g.), identical with that prepared by the previous method.

Ethyl 1-*Bromo*-2-*naphthylthio-oxamate*.—Ethyl 1-bromo-2-naphthyloxamate (22·5 g.) in boiling anhydrous toluene (550 c.c.) was stirred with phosphorus pentasulphide (18 g.) under reflux for 90 minutes and then filtered. On cooling, the filtrate deposited yellow crystals, m. p. 275°, identical with (*B*). The mother-liquor was evaporated to dryness in a vacuum, leaving a yellow solid (23 g.), m. p. 75—78°, which was crystallised several times from alcohol, to give the required *thio*-ester as yellow needles, m. p. 88° (Found: C, 49·6; H, 4·5. $C_{14}H_{14}O_2NSBr$ requires C, 49·7; H, 3·6%).

1-*Bromo*-2-*naphthylthio-oxamic Acid*.—Ethyl 1-bromo-2-naphthylthio-oxamate (1 g.) was shaken with cold 10% potassium hydroxide solution (10 c.c.) for 2 hours. The salt was collected and shaken for 30 minutes with dilute hydrochloric acid, and the precipitated *acid* (0·8 g.) crystallised from dilute alcohol as golden needles, m. p. 123° (decomp.) (Found: C, 45·3; H, 3·3. $C_{12}H_8O_3NSBr$ requires C, 46·5; H, 2·6%).

Naphtho(2′ : 3′-4 : 5)*thiazole*-1′ : 4′-*quinone* (VIII).—2-Chloro-3-amino-1 : 4-naphthaquinone (36 g.) was refluxed with sodium sulphide (45 g.) in water (330 c.c.) for 25 minutes. To the resultant deep-blue solution, formaldehyde (40%; 72 c.c.) was added, followed by glacial acetic acid (36 c.c.) diluted with water (72 c.c.). The mixture was refluxed for 1 hour and filtered. The black residue was extracted several times with boiling alcohol (500 c.c.). On cooling, *naphtho*(2′ : 3′-4 : 5)*thiazole*-1′ : 4′-*quinone* (13 g.), m. p. 245—252°, was deposited. The m. p. was not raised above 245—252° by repeated crystallisation (Found: C, 61·3; H, 2·4; N, 6·5. $C_{11}H_5O_2NS$ requires C, 61·4; H, 2·3; N, 6·5%).

Attempts to reduce this quinone to the parent naphthothiazole by zinc dust distillation in hydrogen, zinc dust fusion (Clar, *Ber.*, 1939, **72**, 1645), stannous chloride in acetic acid (Fries and Kerkow, *Annalen*, 1922, **427**, 281), or hydrogen iodide and phosphorus were unsuccessful.

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UNIVERSITY CHEMICAL LABORATORY,
TRINITY COLLEGE, DUBLIN.

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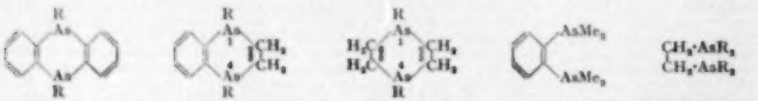
134. *A Synthesis of Derivatives of o-Phenylene-ethylenediarsine and of o-Phenylenetrimethylenediarsine.*

By R. H. GLAUERT and FREDERICK G. MANN.

Derivatives of the above two novel heterocyclic ring systems can readily be obtained from *o*-phenylenebisdimethylarsine, which combines with ethylene dibromide to give 1 : 1 : 4 : 4-tetramethyl-*o*-phenylene-ethylenediarsonium dibromide, and with trimethylene dibromide to give 1 : 1 : 5 : 5-tetramethyl-*o*-phenylenetrimethylenediarsonium dibromide. The thermal decomposition of these salts is being investigated.

IN view of the fact that the heterocyclic ring system of the 5 : 10-disubstituted 5 : 10-dihydroarsanthrens (I) can be reasonably readily synthesised and has high stability (Kalb, *Annalen*, 1921, **423**, 74; Chatt and Mann, *J.*, 1940, 1184), it is surprising that the similar but simpler systems present in the 1 : 4-disubstituted *o*-phenylene-ethylenediarsines (1 : 4-diarsatetrahydronaphthalenes) (II) and in the 1 : 4-disubstituted diethylenediarsines (1 : 4-diarsa*cyclo*hexanes) (III) have hitherto not been recorded. We are engaged in the systematic study of the systems (II) and (III) and of their derivatives, and the present paper records briefly one ready synthesis of the heterocyclic system (II) and of analogous compounds.

For this synthesis we have utilised *o*-phenylenebisdimethylarsine (IV), prepared by the method of Chatt and Mann (*J.*, 1939, 610). This diarsine appeared to be particularly promising

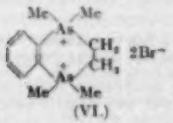


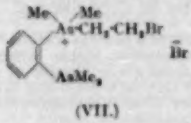
(I.) (II.) (III.) (IV.) (V.)

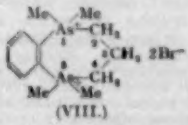
for our purpose, for the two tertiary arsine groups are known to be highly reactive, since Chatt and Mann (*J.*, 1939, 1622) and Allison and Mann (*J.*, 1949, 2915) have shown that the diarsine

has strongly chelating properties. Furthermore, it was considered that a diarsine of this type would lend itself more readily to the projected cyclisation than, for example, the corresponding ethylenebisdialkylarsines (V) (Chatt and Mann, *loc. cit.*), because in the former compound the two tertiary arsenic atoms are held rigidly by the *o*-phenylene group in precisely the position required for ring formation.

Experiment has confirmed these considerations. We find that, when the diarsine (IV) is heated with one molecular equivalent of ethylene dibromide, combination readily occurs to give the highly crystalline *dimethobromide* (VI) of 1 : 4-dimethyl-*o*-phenylene-ethylenediarsine, *i.e.*, 1 : 1 : 4 : 4-*tetramethyl-o-phenylene-ethylenediarsonium dibromide* (1 : 1 : 4 : 4-*tetramethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4-*diarsonianaphthalene dibromide*), m. p. 255°. Evidence that cyclisation has in


(VI.)


(VII.)


(VIII.)

fact occurred and that the product is not the isomeric monoarsonium bromide (VII) is provided in two ways : (*a*) volumetric analysis of a cold aqueous solution of the compound shows that all the bromine is present in the ionic form, and (*b*) the addition of aqueous sodium picrate to such a solution causes the immediate precipitation of the corresponding *dimethopicrate*.

This type of cyclisation is not limited to the formation of six-membered ring systems. We find that the diarsine (IV) when similarly heated with trimethylene dibromide readily gives the highly crystalline bicyclic *dimethobromide* (VIII), *i.e.*, 1 : 1 : 5 : 5-*tetramethyl-o-phenylenetrimethylenediarsonium dibromide* (1 : 1 : 4 : 4-*tetramethyl*-1 : 4-*diarsonia*-2 : 3-*benzcyclohept*-2-*ene dibromide*), m. p. 258°. Here again cyclisation is confirmed by determination of ionic bromine, and by conversion of the dibromide in cold aqueous solution into the corresponding *dimethopicrate*. There is little doubt that, particularly in the seven-membered ring system present in the compound (VIII), the polymethylene chain is " buckled " and that a stable and probably almost strainless ring is thus produced.

It is significant that both the dimethobromides (VI) and (VIII) melt with effervescence. A preliminary investigation of the thermal decomposition of the dimethobromide (VI) indicates that more than one tertiary arsine may thus be formed. We are now investigating this decomposition on a larger scale because the expected simple loss of methyl bromide would give rise to 1 : 4-dimethyl-*o*-phenylene-ethylenediarsine, which should then be capable of conversion into a tricyclic diarsine system by further combination with ethylene dibromide—a synthesis which would be precisely analogous to Mann and Mukherjee's synthesis of the dimethobromide of triethylenediamine by the combination of 1 : 4-dimethylpiperazine and ethylene dibromide (*J.*, 1949, 2298).

Experimental.

o-Phenylenebisdimethylarsine (IV).—By working in an atmosphere of nitrogen, as Chatt and Mann (*loc. cit.*) recommend, this diarsine was prepared from *o*-phenylenebiadichloroarsine, in 82% yield, as a colourless liquid, b. p. 146°/15 mm.

1 : 1 : 4 : 4-*Tetramethyl-o-phenylene-ethylenediarsonium Dibromide* (1 : 1 : 4 : 4-*Tetramethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4-*Diarsonianaphthalene Dibromide*) (VI).—A mixture of the diarsine (IV) (2·7 g.) and dry ethylene dibromide (1·8 g., 1 mol.) was heated under nitrogen at 125—130°, *i.e.*, at just below the b. p. of the dibromide. The mixture soon solidified and after a further 2 hours' heating was cooled, pulverised, washed with ether, and recrystallised from methyl alcohol. The *dibromide* (VI) was obtained as white crystals, m. p. 255° (effervescence) (Found : C, 30·1; H, 4·8; ionic Br, 33·0. $C_{12}H_{22}Br_2As_2$ requires C, 30·4; H, 4·3; ionic Br, 33·7%). The dibromide is freely soluble in cold water, moderately soluble in boiling methyl alcohol, but only sparingly soluble in boiling ethyl alcohol.

When a cold aqueous solution of the dibromide was added to a similar solution of sodium picrate in excess, an immediate precipitation of the *dipicrate* occurred. This salt, when collected, washed, and recrystallised from water, formed yellow crystals, m. p. 236—238° (Found : C, 37·7; H, 3·3; N, 10·6. $C_{24}H_{24}O_{14}N_6As_2$ requires C, 37·4; H, 3·1; N, 10·9%).

1 : 1 : 5 : 5-*Tetramethyl-o-phenylenetrimethylene-diarsonium Dibromide* (1 : 1 : 4 : 4-*Tetramethyl*-1 : 4-*diarsonia*-2 : 3-*benzcyclohept*-2-*ene Dibromide*) (VIII).—This compound was prepared similarly to the previous dibromide, from the diarsine (6·1 g.) and trimethylene dibromide (2·15 c.c., 1 mol.) at 156—160°. Formation of a solid product first became apparent when the bath-temperature reached 135°. The *dibromide*, after recrystallisation from methyl alcohol, formed colourless hygroscopic crystals, m. p. 258° (effervescence) (Found : C, 32·0; H, 4·5; ionic Br, 32·6. $C_{13}H_{22}Br_2As_2$ requires C, 32·0; H, 4·6; ionic Br, 32·8%). This dibromide is freely soluble in cold water, but only very slightly soluble in boiling ethyl alcohol. A mixture of this compound and the dibromide (VI) had m. p. 248° (effervescence).

The corresponding *dipicrate*, prepared as before from a cold aqueous solution of the dibromide

differed from the previous dipicrate in that it was almost insoluble in boiling water, methyl and ethyl alcohols. It was therefore collected, washed with water, and dried, and thus obtained as a yellow powder, m. p. 260° (Found: C, 38·5; H, 3·5; N, 10·7. $C_{32}H_{24}O_{12}N_8As_2$ requires C, 38·25; H, 3·3; N, 10·7%).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 24th,* 1949.]

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135. *Organo-lead Compounds. Part III.* N-*Trialkylplumbisulphonamides.*

By B. C. SAUNDERS.

A large variety of lead compounds of a new type, $RSO_2{\cdot}NR'{\cdot}PbR''_2$, has been prepared by two methods. They are highly crystalline, stable, compounds and all possess powerful sternutatory properties; many of them are intolerable at a concentration of $1 : 10^9$. They are, therefore, more potent than the simpler trialkyl-lead salts already described in this series of papers. The most effective are *N-tri-n-propylplumbimethane-* and *tri-n-propylplumbibenzene-sulphonamide*.

In 1940 McCombie and Saunders reported to the Ministry of Supply a new type of compound, namely, *N-triethylplumbitoluene-*p*-sulphonamide*, $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3$ (I), a colourless, stable, crystalline compound, recrystallisable from benzene and several other non-polar solvents. We prepared it in 73% yield by heating the sodio-derivative of toluene-*p*-sulphonamide with triethyl-lead chloride in alcohol:

$$C_6H_4Me{\cdot}SO_2{\cdot}NH\boxed{Na + Cl}PbEt_3 = C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3 + NaCl$$
(I.)

The compound had the lead content required for the formula (I) and was decomposed by passage of gaseous hydrogen chloride into its suspension in ether, giving pure toluene-*p*-sulphonamide and diethyl-lead dichloride. The latter was almost certainly a secondary product, the primary product being triethyl-lead chloride which is known to give the dichloride when its dilute ethereal solution is kept in the presence of excess of hydrogen chloride. Cleavage of (I) is therefore expressed as:

$$C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3 + HCl \longrightarrow C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + PbEt_2Cl$$

Examined as a sternutator by spraying its alcoholic solution, the sulphonamide (I) proved to be the most effective lead sternutator tested till then, being considerably more potent than the trialkyl-lead salts described in Parts I and II (*J.*, 1949, 919, 2983). It was intolerable at a concentration of $1 : 10^9$. Similar syntheses gave *N-triethylplumbibenzenesulphonamide, tri-n-propylplumbitoluene-*p*-sulphonamide, and tri-n-propylplumbibenzenesulphonamide*, all stable crystalline compounds and, as expected, the introduction of the tri-*n*-propyl grouping increased the sternutatory action (see Part I, *loc. cit.*). For example, tri-*n*-propylplumbibenzenesulphonamide was a particularly powerful sternutator and at a concentration of $1 : 10^9$ all the observers were forced to leave the testing-chamber after an exposure of only 40 seconds (sternutatory grade, 3; cf. Part I). In addition to its action on the nose, throat, chest, and gums, the compound produced irritation on the fingers and faces of some of the workers who undertook its preparation, particularly on a large scale.

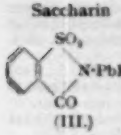
In efforts to simplify the preparation it was found (1941) that mixing cold alcoholic solutions of tri-*n*-propyl-lead hydroxide and benzenesulphonamide and then adding water precipitated *N*-tri-*n*-propylplumbibenzenesulphonamide, practically pure even before recrystallisation, and in almost quantitative yield:

$$PbPr_3{\cdot}OH + C_6H_5{\cdot}SO_2{\cdot}NH_2 = C_6H_5{\cdot}SO_2{\cdot}NH{\cdot}PbPr_3 + H_2O$$

This method had wide application and gave excellent yields, particularly when the sulphonamide was markedly "acidic."

A variety of compounds of the type $R{\cdot}SO_2{\cdot}NR'{\cdot}PbR''_3$ was then prepared in which R = Me, Ph, *o*-C_6H_4Me, *p*-C_6H_4Me, or *p*-$NH_2{\cdot}C_6H_4$, R′ = H, Ph, *p*-C_6H_4Cl, or *p*-C_6H_4Br, and R″ = Et or Pr^n. These were, without exception, powerful sternutators, the most effective being *tri-n-propylplumbimethanesulphonamide*, $Me{\cdot}SO_2{\cdot}NH{\cdot}PbPr_3$, which was extremely unpleasant at a concentration of $1 : 2{\cdot}5 \times 10^9$ (sternutatory grade 3+). In addition, its lower molecular weight and high solubility in alcohol and other organic solvents increased its applicability.

Saccharin reacted readily in cold alcohol with triethyl-lead hydroxide, giving *o-sulphobenzoic triethylplumbi-imide* (III). This and the corresponding *tri-n-propyl* derivative, like the acylic sulphonamides, were powerful sternutators, being intolerable at a concentration of $1 : 10^7$ after only 1½ minutes. Even at this high dilution a "sweet taste" was noticed by the observers.


(III.)

In Parts I and II we reported that an unsaturated grouping intensified the physiological action of an organo-lead compound. For example, triethyl-lead acrylate and tri-*n*-propyl-lead acrylate were more potent than the corresponding saturated salts. In view of the fact that the sulphonamide grouping also increases sternutatory action, it was decided to combine the two "active" groups in one molecule. We accordingly prepared *N-triethylplumbiethylenesulphonanilide*, $CH_2{=}CH{\cdot}SO_2{\cdot}NPh{\cdot}PbEt_3$, by the action of triethyl-lead chloride on the *sodio*-derivative of ethylenesulphonanilide. This sodium salt was soluble in alcohol and reacted smoothly. In this instance a purer product was obtained than when triethyl-lead hydroxide and the free ethylene sulphonanilide were used, as the latter anilide did not appear to be sufficiently acidic to react completely with the hydroxide. Although *N*-triethylplumbiethylenesulphonanilide gave an almost intolerable atmosphere at a concentration of $1 : 10^9$, it did not show the expected increased potency compared with the simpler compounds.

As an example of a compound containing two $-SO_2{\cdot}NR{\cdot}PbR'_3$ groupings in the molecule, we prepared *methanedi-(N-triethylplumbisulphonanilide)* (IV), a powerful sternutator, but not exhibiting outstanding properties.

It should be pointed out that no definite chemical evidence has been produced to decide between formulæ (V) and (VI) for these compounds. Both would account for the cleavage by

$CH_2(SO_2{\cdot}NPh{\cdot}PbEt_3)_2$ (IV.) $\quad R{\cdot}SO_2{\cdot}NR'{\cdot}PbR''_3$ (V.) $\quad R{\cdot}SO(NR')\cdot O{\cdot}PbR''_3$ (VI.)

hydrogen chloride into the parent sulphonamide and the trialkyl-lead chloride. The point could be decided by *X*-ray analysis, and it is hoped that this will be undertaken in the near future.

Experimental.

N-Triethylplumbitoluene-p-sulphonamide.—Toluene-*p*-sulphonamide (3·4 g.) was dissolved in alcohol, and sodium (0·5 g.) was added. The white flaky precipitate produced was filtered off, washed with alcohol, and dried. To this sodio-derivative (1·93 g.), suspended in alcohol, triethyl-lead chloride (3·3 g.) was added and the whole heated under reflux for 20 minutes. The product was then cooled and filtered, and to the filtrate water was added until the solid *triethylplumbitoluene-p-sulphonamide* crystallised out. After being washed with water, dried, and recrystallised from benzene, it had m. p. 127° (Found: Pb, 44·53. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

Cleavage by hydrogen chloride. (*a*) Triethylplumbitoluene-*p*-sulphonamide was suspended in a *large* volume of ether, and dry hydrogen chloride passed in. The substance dissolved and, after saturation, the solution was set aside. Diethyl-lead dichloride separated (Found: Pb, 62·2. Calc. for $C_4H_{10}Cl_2Pb$: Pb, 61·9%).

(*b*) Triethylplumbitoluene-*p*-sulphonamide was suspended in the *minimum* volume of ether and treated as in (*a*). A lead-free solid separated rapidly and had m. p. 138°. It was shown to be toluene-*p*-sulphonamide.

N-Triethylplumbibenzenesulphonamide.—Prepared as above, but by use of molecular quantities of sodiobenzenesulphonamide and triethyl-lead chloride, and recrystallised from benzene, the *sulphonamide* had m. p. 132° (Found: Pb, 45·9. $C_{12}H_{21}O_2NSPb$ requires Pb, 46·0%).

N-Tri-n-propylplumbitoluene-p-sulphonamide.—Sodiotoluene-*p*-sulphonamide (3·6 g.) was suspended in alcohol and tri-*n*-propyl-lead chloride (6·5 g.) was added. Subsequent treatment as above, and recrystallisation from light petroleum (b. p. 80—100°) gave the *amide*, m. p. 100—101° (Found: Pb, 41·1. $C_{16}H_{29}O_2NSPb$ requires Pb, 40·9%).

N-Tri-n-propylplumbibenzenesulphonamide.—(*a*) Prepared and purified as in the preceding paragraph, *N-tri-n-propylplumbibenzenesulphonamide* (73%, crude) had m. p. 96° (Found: Pb, 41·6. $C_{15}H_{27}O_2NSPb$ requires Pb, 42·1%).

(*b*) To an alcoholic solution of tri-*n*-propyl-lead hydroxide (from 3·7 g. of the chloride) was added an alcoholic solution of benzenesulphonamide (1·6 g.). Water was added, and after 10 minutes the product was filtered off. 118 G. of crude but almost pure material were recrystallised, yielding 101 g. of the pure sulphonamide, m. p. 93·5—94·5°. 5 C.c. of alcohol dissolved 3·2 g. of the sulphonamide at 15°, and after 6 days the substance was reprecipitated unchanged (m. p. 93·5—94·5°) by the addition of water.

Tripropylplumbitoluene-*p*-sulphonamide, triethylplumbibenzenesulphonamide, and triethylplumbitoluene-*p*-sulphonamide were also prepared by method (*b*), from the calculated quantities of hydroxide and sulphonamide.

N-Triethylplumbimethanesulphonamide.—Methanesulphonamide (0·95 g.) was dissolved in hot benzene and mixed with triethyl-lead hydroxide (3·11 g.) dissolved in benzene. The mixture was heated under reflux for 30 minutes on a water-bath. After cooling, a very small quantity of a solid separated and was

recrystallised from aqueous alcohol; this decomposed at 197° (Found: Pb, 36·2%). To the filtrate light petroleum was added to precipitate the white crystalline *triethylplumbimethanesulphonamide* which, recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 97° (Found: Pb, 53·4. $C_7H_{19}O_2NSPb$ requires Pb, 53·4%).

N-Tri-n-propylplumbimethanesulphonamide.—Freshly prepared moist silver oxide (2·8 g.) was suspended in benzene and a small quantity of alcohol added. To this was added tripropyl-lead chloride (3·7 g.) dissolved in benzene, and the mixture shaken and then filtered. The filtrate was added to methanesulphonamide (0·95 g.) dissolved in hot benzene, and the procedure of the previous experiment then followed. The *amide* had m. p. 67° (Found: Pb, 48·1. $C_{10}H_{25}O_2NSPb$ requires Pb, 48·2%).

N-Triethylplumbimethanesulphonanilide.—Benzene solutions of methanesulphonyl chloride (3·42 g.) and aniline (5·52 g.) were mixed. After 20 minutes, light petroleum (b. p. 40—60°) was added, and the precipitated mixture of aniline hydrochloride and methanesulphonanilide was boiled with benzene and filtered. To the benzene filtrate, light petroleum was added. Methanesulphonanilide, m. p. 100°, separated (Found: C, 49·6; H, 5·6. Calc. for $C_7H_9O_2NS$: C, 49·1; H, 5·3%). The methanesulphonanilide (0·85 g.), dissolved in alcohol, was added to triethyl-lead hydroxide (1·55 g.) and set aside for 30 minutes. The white crystalline *triethylplumbimethanesulphonanilide* which separated on the addition of water was recrystallised from benzene–light petroleum (b. p. 40—60°), and had m. p. 115·5° (Found: Pb, 44·1. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

N-Triethylplumbisulphanilamide.—A solution of sulphanilamide (1·72 g.) in alcohol was added to a solution of triethyl-lead hydroxide (3·12 g.) in alcohol. After 30 minutes the mixture was filtered, and to the filtrate water was added. The colourless *triethylplumbisulphanilamide* which separated was recrystallised from alcohol and then had m. p. 171° (Found: Pb, 43·9. $C_{12}H_{22}O_2N_2SPb$ requires Pb, 44·53%).

N-Tri-n-propylplumbisulphanilamide.—Prepared similarly, the alcoholic solution of the hydroxide being made by shaking the chloride (3·7 g.) in alcohol with moist silver oxide (2·8 g.) for 10 minutes before filtration, *tri-n-propylplumbisulphanilamide* had m. p. 101° after recrystallisation from benzene (Found: Pb, 40·9. $C_{18}H_{34}O_2N_2SPb$ requires Pb, 40·9%).

o-Sulphobenzoic Triethylplumbi-imide.—A solution of triethyl-lead hydroxide (3·11 g.) in alcohol was added to an alcoholic solution of saccharin (1·8 g.). After 30 minutes the mixture was cooled in ice-water, and water added until a turbidity was produced. On scratching of the vessel, a white solid separated which was recrystallised from a mixture of benzene and light petroleum (b. p. 60—80°). The *lead* derivative was thus obtained as colourless needles, m. p. 135°, containing nitrogen and sulphur (Found: Pb, 44·4. $C_{13}H_{19}O_3NSPb$ requires Pb, 44·1%).

The compound was dissolved in ether and dry hydrogen chloride passed in. Crystals of saccharin separated and, on storage, diethyl-lead dichloride gradually separated from the filtrate.

o-Sulphobenzoic Tri-n-propylplumbi-imide.—Prepared from alcoholic solutions of tripropyl-lead hydroxide (from the chloride) and saccharin, and recrystallised from benzene–light petroleum (b. p. 60—80°), the *imide* had m. p. 130° (Found: Pb, 39·4. $C_{16}H_{25}O_3NSPb$ requires Pb, 40·0%).

N-Triethylplumbitoluene-p-sulphonanilide.—Prepared from the sulphonanilide (2·51 g.) and triethyl-lead hydroxide (3·12 g.) in alcohol, and recrystallised from aqueous alcohol, the *sulphonanilide* had m. p. 134° (Found: Pb, 37·6. $C_{19}H_{27}O_2NSPb$ requires Pb, 38·35%).

N-Tri-n-propylplumbitoluene-p-sulphonanilide.—Prepared similarly to the corresponding sulphanilamide, from the chloride (3·7 g.) and the sulphonanilide (2·51 g.), and recrystallised from aqueous alcohol, this *anilide* had m. p. 104° (Found: Pb, 35·0. $C_{25}H_{39}O_2NSPb$ requires Pb, 35·6%).

N-Triethylplumbitoluene-o-sulphonamide.—Prepared from toluene-o-sulphonamide and triethyl-lead hydroxide, and recrystallised from aqueous alcohol, the *amide* had m. p. 133° (Found: Pb, 44·6. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

N-Triethylplumbitoluene-p-sulphon-p′-chloroanilide.—Prepared from alcoholic solutions of toluene-*p*-sulphon-*p*′-chloroanilide and triethyl-lead hydroxide, the *lead* derivative was recrystallised from benzene and light petroleum, and had m. p. 111·5° (Found: Pb, 36·05. $C_{19}H_{26}O_2SNClPb$ requires Pb, 36·1%).

N-Tri-n-propylplumbitoluene-p-sulphon-p′-chloroanilide, m. p. 123° (Found: Pb, 33·5. $C_{25}H_{38}O_2NSClPb$ requires Pb, 33·6%), and *triethylplumbitoluene-p-sulphon-p′-bromoanilide*, m. p. 117° (from benzene) (Found: Pb, 33·15. $C_{19}H_{26}O_2NSBrPb$ requires Pb, 33·48%), were similarly prepared.

Sodium Ethane-1 : 2-disulphonate (cf. *Annalen*, 1880, **148**, 96, and *J.*, 1922, 120).—The calculated quantities of ethylene dibromide and sodium sulphite ($7H_2O$) were heated under reflux with the minimum amount of water needed to dissolve the sulphite. After 3 hours, the mixture was evaporated to crystallisation, and the solid obtained was dried at 120°. Yield, 75%.

Ethanedisulphonyl Chloride.—To the crude sodium salt, phosphorus pentachloride (2 mols.) was added, and the reaction completed by careful warming. The phosphorus oxychloride was distilled off at 15 mm. and the residue ground with ice and extracted with ether. The ethereal extract was dried (Na_2SO_4) and evaporated. The product, recrystallised from light petroleum (b. p. 100—110°), had m. p. 91° (yield 55%).

Ethylenesulphonanilide.—The above sulphonyl chloride (25 g.) was dissolved in ether (30 c.c.), and aniline (31 g.), also in ether (20 c.c.), was added. (If excess of aniline was used, side-reactions took place.) Heat was evolved, and when the addition was complete the mixture was boiled until no more sulphur dioxide was evolved. The precipitated aniline hydrochloride was filtered off and washed with ether. The ethereal solutions were extracted with hydrochloric acid and dried (Na_2SO_4), the ether was distilled off, and the residue recrystallised from alcohol; it had m. p. 69° (yield 55%).

Sodioethylenesulphonanilide.—Ethylenesulphonanilide (11 g.) was dissolved in aqueous sodium hydroxide solution (25 c.c.; 10%) by warming. The solution was filtered and cooled in ice, and the crystalline precipitate which formed was filtered off and dried on a porous plate. This product was washed with ether, again filtered, and dried *in vacuo* over concentrated sulphuric acid.

The crude product was readily soluble in alcohol, but was recrystallised by adding a small quantity of light petroleum (b. p. 60—80°) to a hot alcoholic solution, filtering this solution while hot and then cooling it in ice. The crystalline *sodioethylenesulphonanilide* was dried *in vacuo* over calcium chloride.

The yield of pure product was 2 g. (16%) (Found: C, 46·6; H, 3·9; N, 7·1. $C_{14}H_{14}O_3NSNa$ requires C, 46·8; H, 3·9; N, 7·8%). The compound was readily soluble in water or alcohol, slightly soluble in acetone, and insoluble in ether, chloroform, or benzene. When the compound was heated slowly the m. p. was sharp (69°; this is the m. p. of the original ethylenesulphonanilide). On further heating of the sodio-derivative, fusion was followed by decomposition and charring, and finally a white residue of sodium sulphate remained.

An aqueous solution, on acidification with dilute sulphuric acid, gave a white precipitate of the original sulphonanilide (m. p. 69°).

N-Triethylplumbiethylenesulphonanilide.—Triethyl-lead chloride (1·2 g.) in alcohol (10 c.c.) and sodioethylenesulphonanilide (0·75 g.) in alcohol (10 c.c.) were mixed and kept at room temperature for 18 hours. Sodium chloride (0·2 g., theoretical yield) was filtered off, and the filtrate poured into water. The white precipitate which separated was filtered off, washed with water, and dried *in vacuo*. The crude *lead* derivative recrystallised as colourless leaflets from light petroleum (b. p. 100—120°) (Found: N, 3·0. $C_{14}H_{29}O_3NSPb$ requires N, 2·95%) (yield 1 g., 55%). When heated gradually, it melted sharply at 116°. When heated in the open in bulk it decomposed with a mild explosion.

Methanedisulphonyl Chloride.—Methanedisulphonic acid was prepared from acetylene and fuming sulphuric acid by the method of Schroeter (*Annalen*, 1919, **418**, 183). To the dehydrated acid (30 g.), phosphorus pentachloride (48 g.) was added in small quantities. When the addition was complete, the mixture was heated on a water-bath for 15 minutes and then the phosphorus oxychloride was distilled off at 42°/20 mm. The residue on distillation at 143°/20 mm. gave the pure disulphonyl chloride (20 g., 83%).

Methanedisulphonanilide.—Aniline (9·3 g.) in benzene (50 c.c.) was added to methanedisulphonyl chloride (5·3 g.) in benzene (35 c.c.). The mixture was boiled under reflux for 10 minutes, cooled, shaken with sodium hydroxide (4 g.) in water (25 c.c.), and filtered through sintered glass to remove a slight precipitate. The aqueous layer was separated, extracted with more benzene, and then acidified with dilute hydrochloric acid. The precipitate was purified by repeated dissolution in dilute sodium hydroxide solution, washing with benzene, and reacidification. The disulphonanilide thus obtained (3·8 g., 50%) was dried *in vacuo* over solid potassium hydroxide and paraffin wax.

Methanedi-(N-triethylplumbisulphonanilide).—Triethyl-lead hydroxide (2 g.) was added to methanedisulphonanilide (1 g.) in a mixture of water (10 c.c.) and alcohol (10 c.c.), and heated till clear. The solution was filtered while hot, and on cooling colourless crystals were obtained and recrystallised from aqueous alcohol. *Methane di-(N-triethylplumbisulphonanilide)* was obtained as long colourless needles, insoluble in water, soluble in alcohol and in hot benzene. The compound did not melt, but sintered at 71° and decomposed at 180° with effervescence. For lead analysis (see Part I, *loc. cit.*) the compound was first decomposed by nitric acid in a sealed tube (Found: Pb, 44·9. $C_{31}H_{62}O_4N_2S_2Pb_2$ requires Pb, 45·4%).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 24th*, 1949.]

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136. *Steroids and the Walden Inversion. Part VI. Reduction of Cholest-5-en-3-one with Lithium Aluminium Hydride.*

By C. W. SHOPPEE and G. H. R. SUMMERS.

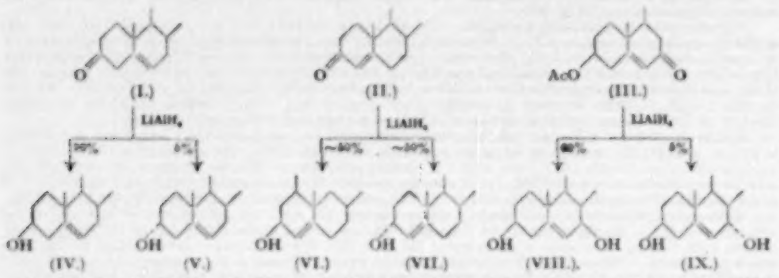
Cholest-5-en-3-one by reduction with lithium aluminium hydride gives unexpectedly much cholesterol and very little *epi*cholesterol; the stereochemical course of the reduction is compared with that of other steroid ketones.

LITHIUM ALUMINIUM HYDRIDE (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199) is a valuable reagent for reduction of variants of the carboxyl group: R—CO—X ⟶ R·CH_2·OH (X = H, OH, OR′, Cl) (Nystrom and Brown, *ibid.*, pp. 1197, 1548). Further, ketones give secondary alcohols, whilst amides yield primary amines (Uffer and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397), but simple ethylenic linkages are unaffected.

Reduction of cholest-5-en-3-one (I) without alteration of the position of the double bond can be carried out only in neutral media, since this compound is readily isomerised, *e.g.*, by simple filtration in pentane solution through non-neutralised aluminium oxide, to cholest-4-en-3-one (II). Partial hydrogenation of (I) with Raney nickel in *cyclo*hexane yields considerable but variable quantities of *epi*cholesterol (V) (Ruzicka and Goldberg, *Helv. Chim. Acta*, 1936, **19**, 1407); since reduction with lithium aluminium hydride has been observed sometimes to offer advantages over catalytic hydrogenation (cf. Plattner *et al.*, *ibid.*, 1949, **32**, 265; Salamon, *ibid.*, p. 1306), we have used this reagent to reduce (I). Reduction proceeds smoothly to give cholesterol (IV) and *epi*cholesterol (V) but the yield of the latter is only about 5%.

The one-sided stereochemical course in the reduction of (I) is surprising since similar reduction of cholest-4-en-3-one (II) leads to approximately equal quantities of the epimeric cholest-4-en-3-ols • (McKennis, jun., and Gaffney, *J. Biol. Chem.*, 1948, **175**, 217); this result has been

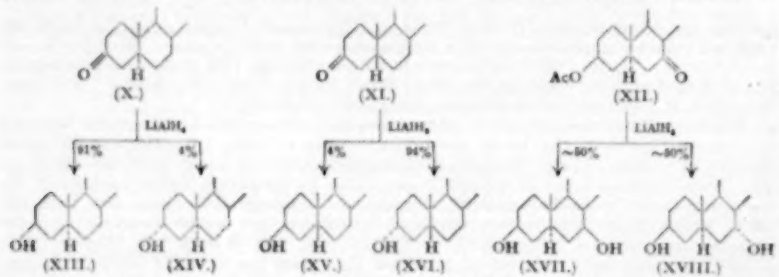
confirmed by Plattner *et al.*, (*loc. cit.*). On the other hand, it has recently been reported that reduction of 7-ketocholesteryl acetate (III) with lithium aluminium hydride proceeds largely in one stereochemical direction to give mainly cholest-5-ene-3β : 7β-diol (VIII) accompanied by 5% of cholest-5-ene-3β : 7α-diol (IX) (Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, **1949**, **71**, 2226).



In reduction by lithium aluminium hydride the active entity appears to be the anion $AlH_4^{\ominus}$ and, since in the reductive fission of epoxides attack at carbon is accompanied by inversion of configuration, it has been suggested that the reaction is a bimolecular nucleophilic replacement, S_N2 (Trevor and Brown, *ibid.*, p. 1675). Reduction of a carbonyl group is a bimolecular addition reaction, so that steric factors should operate (cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173).

Although the presence in (I), (II), and (III) of a double bond at the bridgehead ensures that the lower portions of rings A and B are essentially flat, steric hindrance by the angular methyl group at $C_{(10)}$, arising from repulsion by the electrons of the three C–H bonds, might impede frontal as compared with rearward attack at $C_{(3)}$ by the anion $AlH_4^{\ominus}$. Such hindrance would be consistent with the predominance of the 3β-hydroxy-epimeride (IV) and the 7β-hydroxy-epimeride (VIII), but would be expected also to lead to production of (VI) as the major epimeride.

We have also examined the reduction by lithium aluminium hydride of cholestan-3-one (X) and coprostan-3-one (XI); the former gives cholestanol (XIII) with ~4% of *epi*cholestanol (XIV), whilst the latter yields *epi*coprostanol (XVI) accompanied by ~4% of coprostanol (XV). These results closely resemble those obtained by catalytic hydrogenation in neutral media (Diels and Abderhalden, *Ber.*, 1906, **39**, 884; Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407). The production of (XIII) as principal product is consistent with lesser hindrance at $C_{(3)}$ by the angular methyl group at $C_{(10)}$; in the favoured formation of (XVI) this is not the case, unless the numerous constellations accessible to rings A and B in derivatives of coprostane (Shoppee, *Ann. Reports*, 1946, **43**, 209) combine effectively to eliminate steric hindrance by the angular methyl group at $C_{(10)}$. If hindrance by the hydrogen atom at $C_{(5)}$ is envisaged, as in discussion of the differential rates of alkaline hydrolysis [S_N2] of the 3-acyl derivatives of the alcohols (XIII—XVI) (Ruzicka, Furter, and Goldberg, *Helv. Chim. Acta*, 1938, **21**, 498), then frontal attack by the anion $AlH_4^{\ominus}$ at $C_{(3)}$ in (X), and similar but rearward attack in (XI), should be the less hindered, leading



* Formerly called "allocholesterol" and "*epi*allocholesterol."

respectively to predominant production of (XIV) not (XIII), and (XV) not (XVI). From both points of view it is curious that in the cholestane series, where ring B is certainly a rigid chair-form, it has been found that reduction of 7-ketocholestanyl acetate (XII) with lithium aluminium hydride gives approximately equal quantities of cholestane-3β : 7β-diol (XVII) and of the 3β : 7α-diol (XVIII) (Fieser, Fieser, and Chakravarti, *loc. cit.*; cf. Wintersteiner and Moore, *J. Amer. Chem. Soc.*, **1943**, **65**, 1503).

Finally, it may be remarked that asymmetric induction at $C_{(8)}$ by the other six nuclear asymmetric centres might be expected to produce a considerable effect because they occupy fixed positions, relative to $C_{(8)}$, in a polycyclic system; for the same reason variation of such an effect in opposite senses would not be expected.

Experimental.

(M. p.s were determined thermo-electrically on a Kofler block, and are therefore corrected; limit of error ±2°. All solvents were rigorously purified and dried.)

Cholest-5-en-3-one (I).—This was prepared by the method of Butenandt and Schmidt-Thomé (*Ber.*, 1936, **69**, 882; cf. Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244); the crude product, m. p. 120—124°, is readily purified by dissolution in pentane, filtration of the solution through a column of neutralised aluminium oxide * (activity II—III, 30 × wt. of the crude product) prepared in pentane, and subsequent washing with pentane. The material so eluted, by a single recrystallisation from acetone or ethanol, gave the ketone as needles, m. p. 127°.

Reduction with lithium aluminium hydride. To a vigorously stirred solution of lithium aluminium hydride (2·17 g.) in ether (150 c.c.) cholest-5-en-3-one (I) (m. p. 127°; 2·56 g.), dissolved in ether (100 c.c.), was added during 25 minutes. The mixture was stirred for 2 hours with addition of ether from time to time, the solution becoming opaque; thereafter the reaction-flask was cooled in ice, and excess of lithium aluminium hydride destroyed with ice-cold 0·1*N*-sulphuric acid. The ethereal layer was separated, the acidic solution extracted twice with ether, and the combined ethereal solutions washed with water, sodium hydrogen carbonate solution, and again with water, dried (Na_2SO_4), and evaporated to give a white solid (2·56 g.; m. p. 133—138°). A portion (326 mg.) of the reduction product, dissolved in ethanol (50 c.c.), was treated with a warm 1% solution of digitonin in 95% ethanol (200 c.c.). After being kept overnight, the precipitate of cholesterol digitonide was filtered off and dried (1·2363 g., ≡ 295 mg. of cholesterol); decomposition of the digitonide by dissolution in pyridine (15 c.c.) and precipitation of digitonin with ether (200 c.c.), followed by working up of the resulting filtrate, gave cholesterol (290 mg.), m. p. 148° after crystallisation from ethanol. The original alcoholic filtrate was evaporated completely in a vacuum, and the residue repeatedly extracted with ether; the combined ethereal extracts, after being washed with 2*N*-hydrochloric acid, water, sodium hydrogen carbonate solution, and water, were dried (Na_2SO_4) and evaporated to yield an oil which solidified on cooling. Crystallisation from aqueous ethanol gave *epi*cholesterol (12 mg.) as plates, m. p. 140°, mixed m. p. 140—141°. The proportion of cholesterol in the reduction product was thus 90·5%.

Conversion into Cholest-4-en-3-one (II). Cholest-5-en-3-one (m. p. 127°; 320 mg.), dissolved in pentane (30 c.c.), was filtered through a column of aluminium oxide (Spence type H, activity II, 10 g.) prepared in pentane. Evaporation of the filtrate gave crystalline material (m. p. 80—81° after slight softening; 102 mg.); elution with pentane, with benzene–pentane mixtures, and with benzene gave various fractions (m. p. 73° to 80°; 215 mg.). All fractions were united and recrystallised from ether–methanol to give cholest-4-en-3-one (III), m. p. 80—81°, undepressed by admixture with an authentic specimen.

Reduction of Cholestan-3-one (X) *with Lithium Aluminium Hydride.*—The procedure was that described for cholest-5-en-3-one (I). Cholestan-3-one (m. p. 129—130°; 884 mg.) gave a reduction product (890 mg.); a portion (350 mg.), dissolved in ethanol (100 c.c.), was treated with a warm 1·33% solution of digitonin in 95% ethanol (150 c.c.). The insoluble digitonide was filtered off and gave by appropriate treatment cholestan-3β-ol (319 mg.), double m. p. 125° and 140—141° after crystallisation from methanol. The alcoholic filtrate by evaporation and ether-extraction of the residue yielded cholestan-3α-ol (12 mg.), m. p. 180—181° after crystallisation from aqueous methanol. The proportion of cholestan-3β-ol in the reduction product was thus 91%.

Reduction of Coprostan-3-one (XI) *with Lithium Aluminium Hydride.*—The procedure was that described above; coprostan-3-one (m. p. 59—61°; 950 mg.) gave a reduction product (948 mg.), a portion of which (318 mg.) was separated by treatment with digitonin as above. Only a small precipitate was obtained after storage overnight; this by appropriate treatment gave material (18 mg.) which after crystallisation from methanol yielded coprostan-3β-ol as needles, m. p. 100°, undepressed by admixture with a genuine specimen. Evaporation of the alcoholic filtrate and ether-extraction of the residue furnished crystals (m. p. 102—106° crude); recrystallisation from acetone gave coprostan-3α-ol (300 mg.), m. p. 115—116°, alone or mixed with an authentic specimen. The proportion of coprostan-3-α-ol in the reduction product was thus 94%.

One of us (C. W. S.) acknowledges gratefully a grant from the Royal Society which has partly defrayed the expense of this work, whilst the other (G. H. R. S.) acknowledges the award of a Postgraduate Studentship by the University of Wales and a grant from the Department of Scientific and Industrial Research which enabled him to participate in this investigation.

University College, Swansea, The University of Wales. [*Received, December 7th*, 1949.]

* Prepared by washing with warm aqueous sodium hydroxide and then warm acetic acid and then washed to neutrality with water; reactivated at 200° for 30 hours.

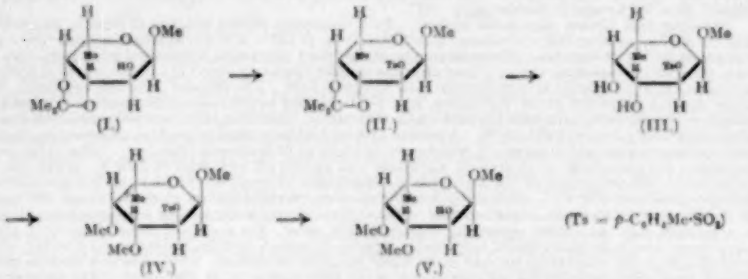
137. 3 : 4-*Dimethyl* L-*Fucose and* 2 : 3-*Dimethyl* L-*Rhamnose.*

By E. E. Percival and E. G. V. Percival.

From 2-*toluene*-p-*sulphonyl* 3 : 4-*isopropylidene* α-*methyl*-L-*fucoside* by mild hydrolysis, methylation, and reduction, 3 : 4-*dimethyl* α-*methyl*-L-*fucoside* and 3 : 4-*dimethyl* L-*fucose* have been prepared. 2 : 3-Dimethyl L-rhamnose has been prepared by a similar route.

The isolation of a dimethyl L-fucose from methylated fucoidin made it desirable to prepare synthetic dimethyl fucoses of known structure. The preparation and properties of the 3 : 4-dimethyl isomer are now recorded.

α-Methyl-L-fucoside was converted into the 3 : 4-*iso*propylidene derivative (I) (MacPhillamy and Elderfield, *J. Org. Chem.*, 1939, **4**, 150) from which 2-*toluene*-p-*sulphonyl* 3 : 4-*isopropylidene* α-*methyl*-L-*fucoside* (II) was prepared. Methanolysis removed the acetone residue (to give III), and methylation then gave 2-*toluene*-p-*sulphonyl* 3 : 4-*dimethyl* α-*methyl*-L-*fucoside* (IV). Reductive fission of the toluene-*p*-sulphonyl residue gave 3 : 4-*dimethyl* α-*methyl*-L-*fucoside* (V) from which by hydrolysis 3 : 4-*dimethyl* L-*fucose* was obtained as the monohydrate, m. p. 75°, $[\alpha]_D$ −118°.



By a similar process 2 : 3-*iso*propylidene α-methyl-L-rhamnoside was converted into 4-*toluene*-p-*sulphonyl* 2 : 3-*dimethyl* α-*methyl*-L-*rhamnoside* from which, by reductive hydrolysis followed by the removal of the glycosidic methyl group, 2 : 3-dimethyl L-rhamnose was prepared as a syrup, $[\alpha]_D$ +40°. This compound prepared by another route (Schmidt, Plankenhorn, and Kübler, *Ber.*, 1942, **75**, 579) is reported to have $[\alpha]_D$ +47·6°. Crystalline 2 : 3-*dimethyl* L-*rhamnose anilide* has been prepared.

By the paper chromatogram the R_6 values (Hirst, Hough, and Jones, *J.*, 1949, 928) of both dimethyl 6-deoxyhexoses have been determined and compared with those of 2-methyl fucose and 4-methyl rhamnose, prepared by the methylation and hydrolysis of the corresponding *iso*propylidene α-methylglycosides. Certain differences between the results obtained and those

Sugar.	R_6.	Sugar.	R_6.
4-Methyl L-rhamnose	0·64; 0·65 (0·57)	2-Methyl L-fucose	0·56 (0·51)
2 : 3-Dimethyl L-rhamnose ...	0·82; 0·83	3 : 4-Dimethyl L-fucose	0·67; 0·68

previously published (Hirst, Hough, and Jones, *loc. cit.*) (in parentheses) emphasise the point made in that publication that such figures are useful as an indication of the methylated sugar concerned, but that direct comparisons on the same chromatogram are essential before identity (in the chromatographic sense) can be established, because of the difficulty of the rigid standardisation of all the variables between different laboratories.

Experimental.

3 : 4-*iso*Propylidene α-*Methyl*-L-*fucoside*.—α-Methyl-L-fucoside (1 g.) in acetone (50 c.c.) containing two drops of acetaldehyde was shaken with anhydrous copper sulphate (11 g.) for 120 hours. One drop of concentrated sulphuric acid was then added, and shaking continued for a further 14 hours. After filtration and neutralisation with potassium carbonate, the solvent was evaporated; the product (0·9 g.), distilled at 95°/0·01 mm., had n_D^{20} 1·4621, $[\alpha]_D^{20}$ −160° (*c*, 1·0 in water). On storage in the refrigerator the product solidified.

2-*Toluene*-p-*sulphonyl* 3 : 4-*iso*Propylidene α-*Methyl*-L-*fucoside*.—The above derivative (0·51 g.) in pyridine (5 c.c.) was treated with powdered toluene-*p*-sulphonyl chloride (1 g.) and kept for 2 days at 15°.

When the mixture was poured on ice a white crystalline solid was obtained which was combined with the product obtained on extraction of the filtrate with chloroform, which was washed with dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. On recrystallisation from methanol a crystalline *product* (0·37 g.), m. p. 182°, $[\alpha]_D^{18}$ −146° (*c*, 1·0 in $CHCl_3$), was obtained (Found: C, 54·7; H, 6·5; OMe, 8·5. $C_{11}H_{22}O_7S$ requires C, 54·8; H, 6·45; OMe, 8·3%).

2-Toluene-p-sulphonyl 3 : 4-*Dimethyl* α-*Methyl*-L-*fucoside*.—Crystalline 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene α-methylfucoside (0·5 g.) was treated with methanolic hydrogen chloride (10 c.c.; 1%) at 70° for 1 hour. After neutralisation with silver carbonate and extraction of the silver residues with ethanol, 2-*toluene-p-sulphonyl* α-*methyl*-L-*fucoside* (0·36 g.), m. p. 158°, $[\alpha]_D^{18}$ −85° (*c*, 1·0 in chloroform), was obtained. This substance was then methylated 4 times with methyl iodide and silver oxide, to give a crystalline *product* (0·4 g.) which, recrystallised from chloroform–light petroleum (b. p. 60—80°), had m. p. 103°, $[\alpha]_D^{18}$ −84° (*c*, 0·7 in chloroform) (Found: C, 53·6; H, 6·6; OMe, 16·6; S, 8·2. $C_{18}H_{28}O_7S$ requires C, 53·3; H, 6·7; OMe, 17·2; S, 8·9%).

3 : 4-*Dimethyl* α-*Methyl*-L-*fucoside*.—The above compound (0·5 g.) in methanol (11 c.c.) and water (5 c.c.) was treated with sodium amalgam (10 g.; 4%) with stirring at 35° during 17 hours. After filtration and extraction with chloroform, the extracts were treated with carbon dioxide for 15 minutes, dried (Na_2SO_4), and freed from organic solvents under diminished pressure. The aqueous residue was neutralised with carbon dioxide, evaporated to dryness, and extracted with ether. From these operations a crystalline *fucoside* was obtained (0·2 g.) which was recrystallised from boiling light petroleum (b. p. 40—60°), to give crystals, m. p. 100°, $[\alpha]_D^{20}$ −213° (*c*, 1·3 in water) (Found: C, 52·1; H, 8·5; OMe, 44·6. $C_9H_{18}O_5$ requires C, 52·4; H, 8·6; OMe, 45·1%).

3 : 4-*Dimethyl* L-*Fucose*.—3 : 4-Dimethyl α-methyl-L-fucoside (0·13 g.) was hydrolysed at 100° with sulphuric acid (15 c.c.; 4%) for 3 hours, whereafter the rotation was constant. After neutralisation with barium carbonate, evaporation to dryness, and extraction with acetone, a crystalline *ether* (0·1 g.) was obtained, having m. p. 82° (from ethanol), m. p. 76° (from chloroform–light petroleum), $[\alpha]_D^{18}$ −118° (*c*, 1·1 in water) (Found: C, 45·9; H, 8·0; OMe, 27·9. $C_9H_{18}O_5.H_2O$ requires C, 45·0; H, 8·6; OMe, 29·5%).

4-*Toluene-p-sulphonyl* 2 : 3-*iso*Propylidene α-*Methyl*-L-*rhamnoside*.—Anhydrous rhamnose (12 g.) was boiled with methanolic hydrogen chloride (150 c.c.; 0·25%) until non-reducing (40 hours) and the syrupy α-methylrhamnoside ($[\alpha]_D$ −48°) isolated. Treatment with acetone as previously described gave a good yield of the *iso*propylidene derivative which distilled at 110°/0·05 mm., n_D^{18} 1·4563, $[\alpha]_D^{18}$ −14° (*c*, 1·1 in acetone). Treatment of this product (3 g.) with toluene-*p*-sulphonyl chloride (5·5 g.) and pyridine (14 c.c.) as described above gave, on pouring of the mixture into ice-water, a crystalline substance which was recrystallised (2·7 g.) from methanol and had m. p. 60°, $[\alpha]_D^{18}$ +22·5° (*c*, 2·0 in methanol) (cf. Levene and Compton, *J. Amer. Chem. Soc.*, 1935, **57**, 2306, who quote m. p. 61—62°, $[\alpha]_D$ +22° in methanol).

4-*Toluene-p-sulphonyl* 2 : 3-*Dimethyl* α-*Methylrhamnoside*.—Removal of the *iso*propylidene residue as described above gave a syrupy *rhamnoside*, $[\alpha]_D$ −73·5° (*c*, 1·4 in chloroform), n_D^{18} 1·5208 (Found: S, 8·9; OMe, 8·0. $C_{14}H_{20}O_7S$ requires S, 9·6; OMe, 9·3%). Methylation with methyl iodide and silver oxide in 3 operations gave a crystalline *ether* (1·9 g.) which, recrystallised from chloroform–light petroleum (b. p. 60—80°), had m. p. 111°, $[\alpha]_D$ −33° (*c*, 2·0 in chloroform) (Found: C, 52·6; H, 6·4; OMe, 25·0. $C_{15}H_{22}O_7S$ requires C, 53·3; H, 6·7; OMe, 25·8%).

2 : 3-*Dimethyl* α-*Methylrhamnoside and* 2 : 3-*Dimethyl Rhamnose*.—Treatment of the above derivative (1 g.) with sodium amalgam as described previously gave 2 : 3-*dimethyl* α-*methylrhamnoside* as a syrup (0·5 g.) which distilled at 110°/0·05 mm. and had n_D^{18} 1·4538, $[\alpha]_D$ −6° (*c*, 2·0 in water) (Found: OMe, 43·2. $C_9H_{18}O_5$ requires OMe, 45·1%). Hydrolysis with sulphuric acid (4%) was complete in 6 hours; 2 : 3-dimethyl rhamnose isolated as above had $[\alpha]_D$ +40° (*c*, 0·7 in water) (Found: OMe, 30·0. Calc. for $C_8H_{16}O_5$: OMe, 32·3%). Treatment of the syrup (0·4 g.) in ethanol (5 c.c.) with aniline (0·4 g.) at 80° for 2 hours followed by evaporation at room temperature gave an *anilide*, m. p. 138—139° (Found: C, 62·3; H, 7·9; N, 4·9; OMe, 21·4. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2; OMe, 23·2%).

Periodate Oxidation [with A. G. Ross].—Estimation of the acetaldehyde liberated on oxidation with periodate (Cameron, Ross, and Percival, *J. Soc. Chem. Ind.*, 1948, **67**, 161) gave only 5·6% of the theoretical amount.

Thanks are expressed to Imperial Chemical Industries Limited for grants.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, December 13th*, 1949.]

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138. *A Theoretical Treatment of the Diels–Alder Reaction. Part I. Polycyclic Aromatic Hydrocarbons.*

By R. D. BROWN.

A new theoretical treatment of the diene synthesis is described. A quantity termed the para-localisation energy is defined, and the results of calculations of this quantity for various pairs of positions in some polycyclic aromatic hydrocarbons are reported. It is shown that these values can be used to predict correctly in every case whether a molecule is reactive, and the observed position of addition. The need for some experimental rate measurements is briefly indicated and the factors neglected and approximations involved in the proposed theory are enumerated.

THE mechanism of the Diels–Alder reaction has been the subject of a number of investigations. In particular it has been shown by stereochemical and kinetic evidence (Bergmann and Eschinazi,

J. Amer. Chem. Soc., **1943**, **65**, 1405; Wassermann, *J.*, **1942**, 612) that the activated complex has a configuration similar to that of the final addition product, *i.e.*, that the two new C–C bonds are formed simultaneously. Theoretical interpretations include Clar's (*Ber.*, **1931**, **64**, 2194; **1932**, **65**, 1521) involving biradical intermediates; an alternative explanation applicable vinyl derivatives of aromatic hydrocarbons has been proposed more recently (Daudel and Pullman, *J. Physique*, **1946**, **7**, 105; *Compt. rend.*, **1945**, **221**, 201; Daudel *et al.*, *Bull. Soc. chim.*, **1948**, **15**, 1202), the dienic properties being associated with certain features of the molecular diagrams obtained by the method of mesomerism. However it is hard to see how either of these ideas could be applied semiquantitatively to determine relative reactivities of various molecules.

Evans and Warhurst (*Trans. Faraday Soc.*, **1938**, **34**, 614) have given a detailed treatment of the kinetics of the dimerisation of butadiene, based on the theory of absolute reaction rates, and assuming the configuration of the activated complex mentioned above. Unfortunately more complex systems are not so susceptible to such a treatment.

The proposed theory combines the advantages of a semiquantitative treatment with applicability to a wider range of molecules. In many ways it is analogous to Wheland's treatment of aromatic substitution (*J. Amer. Chem. Soc.*, **1942**, **64**, 900; Dewar, *J.*, **1949**, 463). For the present we shall consider the addition of one particular dienophil (maleic anhydride) to various conjugated hydrocarbons; it is hoped later to extend the theory to cover the reactions of various dienophils with a particular hydrocarbon.

Assumptions of the Theory.—The formation of an adduct involves the localisation of two of the π-electrons of the conjugated hydrocarbons to form the two new σ C–C bonds. The fundamental assumption of the theory is that the ease of formation of an adduct at a pair of atoms, *m* and *n*, of the hydrocarbon depends only on the energy required to localise two of the π-electrons upon atoms *m* and *n*, *provided that* m *and* n *are orientated favourably*. This latter provision will be taken to be that *m* and *n* must lie para to one another in the case of a polycyclic hydrocarbon. It is proposed to term this energy quantity the *para-localisation energy* * of the pair of atoms *m* and *n*.

The above assumption is equivalent to assuming that the entropy of activation is constant for a given dienophil, and that the important variable part of the potential energy of activation is the para-localisation energy. If such assumptions are valid then it is also likely that the para-localisation energy is the important variable portion of the free energy of reaction; in other words it is likely that the products most rapidly formed will be the most stable. This "consequence" is important because in many cases it is not clear whether the experimentally isolated products are those most rapidly formed or those which are the most stable (from the equilibrium point of view); for the present theory we are justified in interpreting qualitative results in either of these two ways.

Computation of Para-localisation Energies.—The para-localisation energies may be computed by any of the standard approximate quantum-mechanical methods, but the molecular-orbital method, which has several advantages over other methods, particularly when large unsymmetrical molecules are concerned, has been used exclusively in the present work. Clearly from the definition of the para-localisation energy, *P*, we have:

$$P = E_r - E + 2\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where E is the π-electron energy of the original conjugated system, 2α the energy of two isolated π-electrons, and E_r is the total π-electron energy of the one or more separate conjugated systems left when the two π-electrons are localised upon atoms *m* and *n*. In keeping with previous terminology (Brown, *Aust. J. Sci. Res.*, *A*, **1949**, **2**, 566) these conjugated systems will be termed collectively the residual molecule.

The energies E, E_r may be computed by assuming orthogonal atomic orbitals, or by including the overlap integral, whose value is generally assumed to be 0·25. The latter procedure is generally accepted as being more accurate, and it has been proposed (Brown, *Trans. Faraday Soc.*, in the press) to denote energy quantities computed by assuming an overlap integral of 0·25 by primed symbols, quantities computed by assuming orthogonal orbitals being represented by the corresponding unprimed symbols. In addition the former quantities are expressed in terms of the exchange integral, γ, the latter in terms of the exchange integral, β. Thus P', defined by

$$P' = E_r' - E' + 2\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

will be expressed in terms of γ, P, defined by equation (1), in terms of β. In general both P and P' will be listed for each pair of positions, but only P' will be converted into kcal. mol.$^{-1}$, the

* I am indebted to Professor C. A. Coulson for suggesting this name and the symbol *P*.

conversion factor, $\gamma = -34$ kcals., recommended by Dewar (*Trans. Faraday Soc.*, 1946, **42**, 767) being used for this purpose.

P and P' may alternatively be expressed in terms of resonance energies:

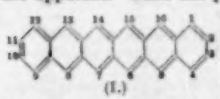
$$P = R - R_r - 2\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$P' = R' - R_r' - 1{\cdot}6\gamma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Before proceeding to the discussion of results obtained for various molecules we may notice a general principle which is apparent from inspection of equations (3) and (4), namely that for any given molecule the most reactive pair of positions will be those giving rise to the most stable residual molecule.

Results.—The results of calculations of P and P' are listed in Tables I—IV. Except where otherwise indicated in the Tables, the resonance energies involved have been calculated by direct solution of the relevant secular determinants. Differences in P' from the value $-2{\cdot}07\gamma$ for the 9 : 10 positions of anthracene have in many cases been converted into "theoretical" ratios of rate constants upon the assumption that $RT = 0{\cdot}6$ kcal. N represents the number of separate conjugated systems comprising the residual molecule. This will be referred to again later.

The para-localisation energies of the linear polyacenes (I) are shown in Table I. Two things are apparent. First the para-localisation energy of the most reactive pair of positions for a given molecule decreases with increasing size of the molecule, pointing to an increase in reactivity with increasing molecular weight. Secondly in any particular molecule the reactivity of successive pairs of "meso"-positions (pairs such as 1 : 4, 5 : 16, 6 : 15 in hexacene being classed as "meso" for convenience in discussion) increases as we move towards the centre of the molecule. From the results for an infinite strip it is clear that a limiting value of the reactivity is rapidly approached in both of these sequences.



(I.)

Many other possible pairs of positions have been excluded from consideration in the Tables by means of the principle that only pairs giving rise to sufficiently stable residual molecules will be reactive, and, on this qualitative principle, the positions listed are the most reactive of all possible pairs in each molecule.

TABLE I.

The Polyacenes.[a]

Molecule.	Positions.	$P(-\beta)$.	P', $(-\gamma)$.	P', kcals.	Relative rate.
Benzene	1 : 4	4·00	2·67	91	*ca.* 10^{-15}
Naphthalene	1 : 4	3·68	2·40	82	*ca.* 10^{-8}
Anthracene	1 : 4	3·63	2·34	80	*ca.* 10^{-7}
	9 : 10	3·31	2·07	70	1
Naphthacene	1 : 4	3·62	2·33	79	—
	5 : 12	3·25	2·01	68	30
Pentacene	1 : 4	3·61	2·33	79	—
	5 : 14	3·23	1·99	68	90
	6 : 13	3·18	1·94	66	1,600
Hexacene (I)	1 : 4	3·61	2·33	79	—
	5 : 16	3·23	1·99	68	90
	6 : 15	3·16	1·92	65	5,000
Infinite strip[b]	*a*	3·611	2·325	79	—
	b	3·223	1·984	67	—
	c	3·151	1·913	65	—
	d	3·132	1·893	64	—
	e	3·126	1·887	64	—
	f	3·124	1·885	64	—
	g	3·124	1·884	64	48,000

[a] N is 2 for all pairs of positions considered here. [b] Values for the limit of the polyacene series were computed by using asymptotic values for the resonance energies, R, R' (results in course of publication). The pairs of positions referred to by *a*, *b*, *c*, . . . are the successive "meso"-positions starting at one end of the strip; for example, on this system the pairs of positions in hexacene numbered 1 : 4, 5 : 16, 6 : 15 would be referred to as *a*, *b*, *c*, respectively.

The results given in Table I explain the experimental findings for the polyacenes. As benzene and naphthalene do not add maleic anhydride (Mameli, Pancotto, and Crestani, *Gazzetta*, 1937, **67**, 669; Alder, "Newer Methods of Preparative Organic Chemistry," 1948, p. 485; Clar, "Aromatische Kohlenwasserstoffe," 1941, p. 12) and anthracene on the other hand undergoes addition at the 9 : 10-positions (Clar, *Ber.*, 1931, **64**, 1682; *op. cit.*, p. 126; Diels and

Alder, *Annalen*, 1931, **486**, 191) it appears that appreciable addition can be detected only when P is less than $-3{\cdot}65$ or P' is less than $-2{\cdot}3\gamma$ (78 kcals./mole). In agreement with prediction naphthacene, pentacene, and hexacene add maleic anhydride at the central "meso"-positions with rapidly increasing ease (Clar, *Ber.*, 1932, **65**, 503; 1931, **64**, 2194; 1939, **72**, 1817).

The critical values of P and P' just mentioned will be seen to predict correctly the course of the Diels–Alder reaction for all polynuclear hydrocarbons for which the experimental facts are known. Strictly, a given critical value of P' should apply only for a given experimental temperature (and possibly solvent) and for a given value of N. However, in the present paper almost all reactive positions correspond to $N = 2$. Also it might be necessary to specify different critical values for different dienophils. The experimental data are not sufficiently numerous to select any particular temperature as standard.

TABLE II.

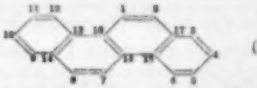
Molecule.	Positions.	N.	$P(-\beta)$.	P', $(-\gamma)$.	P', kcals.
Phenanthrene (II)	1 : 4	2	3·77	2·47	84
	9 : 12	2	4·46	2·88	98
	2 : 12	2	4·51	2·91	99
	4 : 5	1	4·27 [a]	—	—
Chrysene (III)	3 : 6	2	3·74	2·45	83
	8 : 16	2	4·33 [b]	—	—
	7 : 13	2	4·52	2·94	100
	6 : 7	1	4·57 [c]	—	—
3 : 4-Benzphenanthrene (IV)	1′ : 4′	2	3·74	2·45	83
	2 : 12	2	4·25	2·70	92
	1 : 4	2	4·52	2·93	100
	4′ : 13	1	5 [c]	—	—
Picene (V)	1 : 4	2	3·75	2·46	84
	6 : 16	2	4·51	2·92	99
	6 : 7	1	*ca.* 3·80 [c]	—	—
	1 : 14	1	*ca.* 3·97 [c]	—	—

[a] The resonance energy of the residual molecule, R_r, was obtained from Syrkin and Diatkina's data (*Acta Physicochim.*, 1946, **21**, 641). [b] R_r was obtained from Berthier and Pullman's data (*Bull. Soc. chim.*, 1948, **15**, 554). [c] R_r was calculated from the redox potential of the corresponding quinone by an empirical method (in course of publication).

The para-localisation energies of some angular hydrocarbons are listed in Table II. All values listed are greater than those for 1 : 4-addition to naphthalene; this is in agreement with experimental observations (Jones, Gogek, and Sharpe, *Can. J. Research*, *B*, 1948, **26**, 719; Alder, *op. cit.*, p. 485; Clar, *Ber.*, 1932, **65**, 853; Clar and Lombardi, *ibid.*, p. 1413) that phenanthrene and chrysene will not react with maleic anhydride. The possibility of reaction of 3 : 4-benzphenanthrene or picene with maleic anhydride does not seem to have been investigated. The present results indicate that no addition will take place with these hydrocarbons; a result to be expected from the principle that "only molecules containing the anthracene skeleton will react." It will also be noticed that the reactivity, as indicated by the smallest value of the para-localisation energy for each molecule, remains almost constant.

Values of P and P' for some molecules related to anthracene are presented in Table III (it will be noticed that N is 2 for all pairs of positions considered). These indicate that addition will occur in each case, the "meso"-positions of the anthracene portions being attacked preferentially, and the ease of addition decreasing in the sequence: 1 : 2-benznaphthacene, anthracene, 4 : 5-benzchrysene, 1 : 2-benzanthracene, pentaphene, 1 : 2-3 : 4-dibenzanthracene, 1 : 2-7 : 8-dibenzanthracene, 1 : 2-5 : 6-dibenzanthracene, the last two being of almost identical reactivity (calculations to a greater number of significant figures for P' predict relative reaction rates of 1 : 1·07 for these two compounds) so that the actual relative reactivities will probably be more dependent upon factors which are ignored in the present treatment for simplicity (*e.g.*, entropy of activation). This sequence agrees with all available experimental facts. 1 : 2-Benz-

(II.)

 (III.)

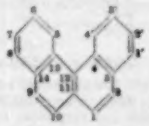
anthracene is more difficultly reactive than anthracene (Clar, *Ber.*, 1932, **65**, 519; "Aromatische Kohlenwasserstoffe," p. 133), in sharp contrast to its isomer, naphthacene (see above). This is

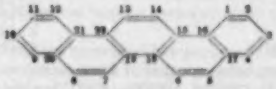
TABLE III.

Molecule.	Positions.	$P(-\beta)$.	P', $(-\gamma)$.	P', kcals.	Relative rate.
Anthracene	1 : 4	3·63	2·34	79	—
	9 : 10	3·31	2·07	70	1
1 : 2-Benzanthracene *	1′ : 4′	3·78	2·49	85	—
	5 : 10	3·41	2·17	74	0·003
	6 : 9	3·64	2·36	80	—
1 : 2-3 : 4-Dibenzanthracene	1′ : 4′	3·82	2·55	87	—
	5 : 10	3·49	2·24	76	0·00006
	6 : 9	3·70	—	—	—
1 : 2-5 : 6-Dibenzanthracene	1′ : 4′	3·79	2·49	85	—
	5 : 10	3·51	2·26	77	0·00002
1 : 2-7 : 8-Dibenzanthracene	1′ : 4′	3·79	2·49	85	—
	5 : 10	3·51	2·26	77	0·00002
Pentaphene (2 : 3-6 : 7-dibenzphenanthrene)	1 : 4	3·67	2·38	81	—
	5 : 14	3·45	2·20	75	0·0006
1 : 2-Benznaphthacene *	1′ : 4′	3·80	2·49	85	—
	5 : 12	3·36	2·11	72	0·1
	6 : 11	3·28	2·03	69	10
	7 : 10	3·64	2·34	79	—
4 : 5-Benzchrysene *	9 : 12	3·74	2·45	83	—
	3 : 6	3·38	2·14	73	0·02
	1′ : 4′	3·64	2·36	80	—

* The resonance energies of these compounds were computed by using an empirical method based upon the concept of "annelation energy" (in course of publication).

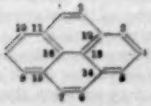
an excellent example of the different effects of linear and angular annelation upon the resonance energy of a polycyclic hydrocarbon (the residual molecule is the same for "meso"-addition to these two hydrocarbons), and can be shown to be related to the difference in mobile order of the 1 : 2- and the 2 : 3-bond in anthracene (results in course of publication). 1 : 2-5 : 6-Dibenzanthracene reacts considerably less readily than anthracene with maleic anhydride (Cook, *J.*, 1931, 3273), and pentaphene adds two molecules of maleic anhydride at a much slower rate than

(IV.) 



(V.)

anthracene, at the positions predicted in Table 3 (Clar, *Ber.*, 1931, **64**, 2195). It will be observed that addition of one molecule of maleic anhydride to the 5 : 14-positions of pentaphene results in a molecule of adduct which in the present treatment must be regarded as anthracene; thus the second addition occurs at the "meso"-positions in the anthracene system, which corresponds to the 8 : 13-positions in the pentaphene system, and so must be expected to take place more rapidly than the addition of the first molecule of dienophil. The experimental data for 1 : 2-benznaphthacene, 4 : 5-benzchrysene, and 1 : 2-3 : 4-dibenzanthracene are also in excellent accord with the theory. Clar and Lombardi (*ibid.*, 1932, **65**, 1419) noted qualitatively that the order of reactivity is that predicted by the present theory. The relative rates deduced from differences in P' will be noticed to be 1,000,000 : 2,000 : 1 but these are expected to be too great because complete localisation is assumed in the activated complex. This makes the calculated values



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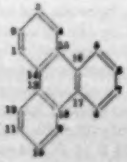

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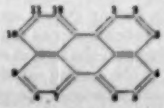
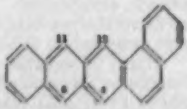


(VIII.)



(IX.)

of P' too great and the effect is not wholly cancelled when differences in P' are considered. Hence when these are converted into kcals. with the conversion factor which is known (Dewar,

Trans. Faraday Soc., 1946, **42**, 767) to give excellent values for resonance energies, the resultant differences in activation energy will necessarily be too great. The predicted relative rates are of course exponential functions of the activation-energy differences and so are very sensitive to the absolute magnitudes of the latter. This could be overcome by choosing a value for γ which gives satisfactory relative rates, but in view of the approximations inherent in the present treatment it is unlikely that anything more reliable than the order of magnitude of relative rates could be estimated by this method. In this connection comparative measurements of the rates of addition for some of the hydrocarbons listed in Table III would be valuable, and the case of 1 : 2-7 : 8- and 1 : 2-5 : 6-dibenzanthracene is particularly interesting in view of the very slight difference ($0{\cdot}0012\gamma$) in P' for these two compounds (see above).

The theoretical results for 1 : 2-benznaphthacene, in addition to predicting the correct reactivity relative to the other related molecules, also lead to the correct conclusion about the position of addition. Thus of the two possible pairs of positions, shown in (IX), which are expected to be reactive on empirical grounds, it is 6 : 11 which undergoes addition, as the present theory predicts. This could not have been predicted by the existing empirical principles.

TABLE IV.

Molecule.	Position.	N.	$P(-\beta)$.	P'. ($-\gamma$).	P'. kcals.
Diphenyl	1 : 4	3	4·38	2·78	95
	2 : 5	2	3·96	2·64	90
	2 : 2′	1	4·33	3·01	102
p-Terphenyl [a]	1 : 4	3	4·39	2·79	95
	2 : 5	2	3·96	2·64 [b]	90
	2′ : 5′	2	3·92	2·62	89
p-Quaterphenyl [a]	1 : 4	3	4·39	2·79	95
	2 : 5	2	3·96 [a]	2·64 [c]	90
	2′ : 5′	2	3·92	2·61	89
Pyrene (VI)	3 : 14	2	4·38 [d]	2·79 [d]	95
	6 : 16	1	4·50 [d]	2·93 [d]	100
	11 : 12	2	5·43 [e]	—	—
Triphenylene [a] (VII)	1 : 4	2	3·79	—	—
	2 : 15	2	4·42	—	—
	13 : 16	2	5·19	—	—
	1 : 12	1	4	—	—
Perylene (VIII)	1 : 12	1	3·92 [d]	2·60 [d]	88

[a] The resonance energies of these molecules were computed from the empirical equations for the conjugation energies (Brown, *Aust. J. Sci. Res., A*, 1949, **2**, 566; other results in course of publication). [b] R' for the residual molecule was calculated from the empirical equation for the conjugation energy, C'. [c] The conjugation energies, C and C', were estimated for calculation of R and R'. [d] The resonance energies of the residual molecules, R_r, R_r', were calculated from C and C'. [e] The value used for the resonance energy of this molecule was that given by Syrkin and Diatkina (*loc. cit.*).

The para-localisation energy of some miscellaneous hydrocarbons are presented in Table IV. From the critical values for P and P' suggested above it would be expected that none of the molecules listed would add maleic anhydride. The experimental observations agree with this prediction in the case of diphenyl and pyrene (Arbuzov, Salmina, and Sharpshinskaya, *Trans. Butlerov Inst. Chem. Tech. Kazan*, 1934, No. 2, 9; Clar, *Ber.*, 1936, **69**, 1683) but at first sight the reaction reported for perylene (Clar, *ibid.*, 1932, **65**, 846) appears to form an exception to the present theory. However it is significant that the product isolated is not the adduct but the corresponding dehydrogenated compound. It seems likely that the factor which produces this product is an irreversible disturbance of the equilibrium between the adduct and its components (and very much in favour of the components as judged by the value of P') by oxidation by the solvent, nitrobenzene. Further weight is lent to this interpretation by Clar's observation that no detectable reaction occurs in boiling xylene, and also that prolonged heating at the relatively high temperature of boiling nitrobenzene was required to obtain a satisfactory reaction.

It may be remarked in passing that the lack of reactivity noted for some of the other molecules considered above may be due to the setting up of an unfavourable equilibrium just as much as due to a very small rate constant because if the value of P or P' is a satisfactory criterion these two phenomena will run parallel (see above).

The above study of some 24 hydrocarbons shows that the proposed theory of the Diels–Alder reaction is completely satisfactory to the present extent of experimental knowledge. The empirical fact that molecules containing the anthracene skeleton are in general reactive and the

more angular molecules unreactive is convincingly explained by the fact that the former can give rise to relatively stable residual molecules whereas the latter cannot. In addition the relative reactivities of reactive hydrocarbons can readily be interpreted; indeed it is possible to interpret these relative reactivities in a general qualitative way, as will be described in a later paper of this series.

Approximations and Neglected Factors.—As mentioned above, variations in the entropy of activation are neglected in the present theory, variations in reaction rate being assumed to be due only to variations in the potential energy of activation. Formation of the activated complex will presumably involve partial localisation of two of the π-electrons of the hydrocarbon, together with two of its carbon atoms, *m* and *n*, which are now linked to the dienophilic portion by incipient σ-bonds. The energy of activation will include the energy of formation of the latter bonds together with energy changes accompanying any change in the spatial configuration of the hydrocarbon portion. The assumption has been made that any such contributions are approximately constant from molecule to molecule, and attention has then been focussed upon variation in the π-electron energy changes.

As the atoms *m* and *n* are not completely localised in the transition state the residual molecule will be more stable than has been assumed above by an amount equal to the conjugation energy of the various separate conjugated systems through atoms *m* and *n*. Qualitatively we might expect this conjugation energy to increase with increase in N, the number of separate systems comprising the residual molecule. Consequently if two pairs of positions have the same para-localisation energy we should expect the one with the greater N to be the more reactive.

Another approximation involved in the present theory is the calculation of the para-localisation energy by an approximate method. However the systems involved are always neutral molecules and Dewar (*Trans. Faraday Soc.*, 1946, **42**, 767) has shown that the molecular-orbital method gives very satisfactory resonance energies in such cases. It will be observed that the proposed theory applies equally well to the "ionic" mechanism favoured by Woodward (*J. Amer. Chem. Soc.*, 1942, **64**, 3058) for the diene synthesis. In the latter case we have merely to replace the assumption that a system of two isolated carbon atoms, each carrying one π-electron, has an energy approximately constant from molecule to molecule, by the analogous assumption that a system of two isolated carbon atoms, one carrying two π-electrons, the other none, has the same property. For convenience the energy of either system may be assumed to be 2α to simplify the values of P and P'.

The para-localisation-energy concept has been applied to some other polycyclic hydrocarbons for which the experimental investigation has not been made. These results and others for vinyl and phenyl derivatives of aromatic hydrocarbons will be presented in Part II.

University of Melbourne, Victoria, Australia. [*Received, October 11th*, 1949.]

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139. *The* Euphorbia *Resins. Part III. The Epimerisation and Dehydration of Euphol.*

By Ralph N. E. Bennett and Frank L. Warren.

Euphone is reduced with difficulty by aluminium *iso*propoxide to give *epieuphol* (hydrogenated to *dihydroepieuphol*), which is not identical with any of the known tetracyclic triterpene alcohols. Similar reduction of dihydroeuphone gave dihydroeuphol. *Euphyl toluene-p-sulphonate* in boiling acetic acid or pyridine gave *euphatrienc* which was hydrogenated to euphene.

In view of the isolation from the *Euphorbia* species of several isomeric tetracyclic triterpene alcohols, $C_{30}H_{50}O$, containing an *iso*propylidene group and an inactive double bond, it became of interest to prepare the hydrocarbon, ketone, and epimeric form of the principal constituent euphol for comparison purposes. Whilst this work was in progress, Roth and Jeger (*Helv. Chim. Acta*, 1949, **32**, 1625) reported the dehydrogenation of euphol and dihydroeuphol to euphone and dihydroeuphone, respectively, which have properties in agreement with our findings. We have observed, however, that these dehydrogenations are effected in higher yields with copper oxide (cf. Diels and Abderhalden, *Ber.*, 1904, **37**, 3099) than with precipitated copper. Euphone is not an αβ-unsaturated ketone since the light-extinction curve which shows $\lambda_{max.}$ 210 mμ. (log $\epsilon_{max.}$ 3·7) and $\lambda_{max.}$ 295 mμ. (log $\epsilon_{max.}$ 1·4) is identical in the ultra-violet with that of euphyl acetate. Dutta and Karimulla (*J. Sci. Ind. Res. India*, 1944, **3**, 212) report that the dried latex from *E. tirucalli* yielded a ketone, $C_{31}H_{48}O$. We have failed to

isolate a ketone from the fresh latex (cf. Haines and Warren, *J.*, 1949, 2554), and this ketone is probably formed during the drying, for the *Euphorbia* latices readily give positive tests for indirect oxidases. This ketone is certainly identical with euphone (see table below), the formula for which follows from the rigid establishment of euphol as $C_{30}H_{50}O$ by McDonald, Warren, and Williams (*J.*, 1949, S 155).

	This paper.	M. p.	Dutta and Karimulla.	M. p.
Euphone	$C_{30}H_{48}O$	117—118°	$C_{31}H_{48}O$	119°
Euphoxime	$C_{30}H_{49}ON$	192—193	Oxime	194—195
Dihydroeuphoxime	$C_{30}H_{51}ON$	205—206	Tetrahydro(?)-oxime	207—208

Catalytic reduction of euphone in the presence of Adams's catalyst at atmospheric pressure gave dihydroeuphone as reported by Roth and Jeger (*loc. cit.*), but under pressure dihydroeuphol was obtained. Attempts to reduce euphone by the Meerwein–Pondorff–Verley reaction, using the standard procedure of refluxing with *iso*propyl alcohol as solvent, gave, even after prolonged treatment, pure euphone in quantitative yield. By carrying out the reaction in toluene (cf. Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 461) or in *iso*butanol (cf. Malcom and Read, *J.*, 1939, 1037) it was possible to obtain small quantities of *epi*euphol, $C_{30}H_{50}O$, m. p. 125°, $[\alpha]_D^{20}$ +22·6°, yielding an *acetate*, m. p. 112—113°, $[\alpha]_D^{20}$ −66°. The small quantity of *epi*euphol was readily eluted from a column of alumina and the residual product, which was more strongly adsorbed, gave no pure substance. The difficulty of reducing euphone by the Meerwein–Pondorff–Verley reaction may be attributed to the keto-group's being sterically hindered, and is interesting in the light of the statement made by Newbold and Spring (*J.*, 1944, 250) that "the ease with which euphol is washed from alumina with light petroleum is remarkable and . . . . this property is probably of constitutional significance."

Catalytic reduction of *epi*euphyl acetate at atmospheric pressure in the presence of Adams's catalyst gave an acetate, m. p. 108—110°, which showed no depression when mixed with starting material (it was at first thought that the dihydro-compound had not been formed). Reduction of *epi*euphol under pressure gave *dihydroepieuphol*, $C_{30}H_{52}O$, m. p. 128—129°, $[\alpha]_D^{20}$ +33·9°, which showed a decided depression when mixed with *epi*euphol. It yielded an *acetate*, $C_{32}H_{54}O_2$, m. p. 111°, $[\alpha]_D^{20}$ −61·2°, which, when mixed with *epi*euphyl acetate, m. p. 112—113°, was depressed only to 105—110°. Attempts to obtain dihydro*epi*euphol by the reduction of dihydroeuphone with aluminium *iso*propoxide or with sodium and *iso*propyl alcohol gave only dihydroeuphol as the isolable product.

It is of interest that attempts to epimerise euphol by boiling *euphyl toluene*-p-*sulphonate* with acetic acid (cf. Plattner and Fürst, *Helv. Chim. Acta*, 1943, **26**, 2266) gave *euphatriene*, which was also obtained by boiling the toluenesulphonate with pyridine. This euphatriene was hydrogenated catalytically to euphene having physical properties identical with those reported by Roth and Jeger (*loc. cit.*) for euphene obtained by Wolff–Kishner reduction of euphone.

Experimental.

(Microanalyses were by Drs. Weiler and Strauss, Oxford. All m. p.s are uncorrected.)

Euphone.—(*a*) Euphol (2 g.) and dry, freshly precipitated copper (4 g.) were heated at 330—340° for 12 minutes, and the product distilled at 180—240°/5 mm. to give a glassy solid. Crystallisation from methanol–acetone and finally from ethanol gave euphone as stout needles, m. p. 117—118°, $[\alpha]_D^{20}$ +78·2° (*c*, 1 in chloroform) (Found: C, 84·65; H, 11·0. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%). Roth and Jeger (*loc. cit.*) give m. p. 119—120°, $[\alpha]_D^{20}$ +69°. *Euphone oxime* crystallised from ethanol in colourless plates, m. p. 192—193°, $[\alpha]_D^{20}$ +7·5° (*c*, 1 in chloroform) (Found: C, 82·0; H, 11·0. $C_{30}H_{49}ON$ requires C, 81·9; H, 11·2%).

(*b*) Euphol (2 g.) was heated to 300° for 15 minutes in an atmosphere of carbon dioxide, and copper oxide (0·4 g.) added slowly. The product in light petroleum (b. p. 50—70°) was chromatographed through alumina (25 g.). Light petroleum (250 ml.) eluted a solid which was crystallised as above to give 1·6 g. of pure euphone. This method was preferred to method (*a*).

Dihydroeuphone.—(*a*) Dihydroeuphol, oxidised with copper oxide as above and crystallised from ethanol, gave dihydroeuphone, m. p. 64°. Roth and Jeger (*loc. cit.*) give m. p. 68°. *Dihydroeuphone oxime* crystallised from ethanol in colourless pearly plates, m. p. 205—206°, $[\alpha]_D^{20}$ +3° (*c*, 1 in chloroform) (Found: C, 82·2; H, 11·65; N, 3·2. $C_{30}H_{51}ON$ requires C, 81·7; H, 11·6; N, 3·2%). (*b*) Catalytic hydrogenation of euphone gave dihydroeuphone identical with the above.

Dihydroeuphol.—(*a*) Euphone (1 g.), hydrogenated with Adams's catalyst at 50 atm. pressure, gave quantitatively dihydroeuphol, m. p. 117—118°, undepressed with authentic specimen. (*b*) Dihydroeuphone (1 g.) was treated with aluminium *iso*propoxide in toluene as described below for the preparation of *epi*euphol. Chromatographic analysis of the product in ether and two crystallisations from methanol gave only dihydroeuphol, as felted needles, m. p. 120—121°, undepressed on admixture with an authentic specimen. (*c*) Dihydroeuphone (250 mg.) and *iso*propyl alcohol (38 ml.) were refluxed with sodium (1·25 g.)

for 1 hour. The solution was poured into water and extracted with ether, and the ethereal extract washed with water and dried. The ethereal solution gave a gum which was treated with acetic anhydride (3 ml.) and pyridine (1·6 ml.) and worked up in the usual way. The product, twice crystallised from methanol, gave dihydroeuphyl acetate, m. p. 122—124°, undepressed on admixture with an authentic specimen.

*epi*Euphol.—(*a*) Euphone (1 g.), freshly distilled aluminium *iso*propoxide (2 g.), and *iso*butyl alcohol (20 ml.) were refluxed in an oil-bath at 160°. After each hour *iso*butyl alcohol (10 ml.) was added, and 10 ml. were allowed to distil off. After 6 such operations a further quantity of aluminium *iso*propoxide (4 g.) was added to replace loss and hasten the reaction. The product was steam-distilled and then acidified with dilute sulphuric acid, and the dried ethereal extract was chromatographed through alumina (20 × 2 cm.). The first 180 ml. eluted a solid (200 mg.), m. p. 117—119°, which, crystallised twice from acetone and twice from methanol, gave *epieuphol* as fine felted needles, m. p. 125°, $[\alpha]_D^{20}$ +22·6° (*c*, 0·9 in chloroform) (Found: C, 84·4; H, 12·0. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Mixed m. p.s with euphol, m. p. 116°, and dihydroeuphol, m. p. 120—121·5°, gave depressions to 88—94° and 90—95°, respectively. Further elution of the column gave a solid, m. p. *ca.* 50—70°, from which a pure component could not be isolated.

(*b*) Euphone (1 g.) and aluminium *iso*propoxide (15 g.) in dry toluene (20 ml.) were refluxed in an oil-bath for 4 hours. Absolute *iso*propyl alcohol was added and then distilled off. The ethereal extract gave a solid which was dissolved in ether and chromatographed through alumina (22 × 2 cm.). The first 100 ml. of ether eluted a solid (200 mg.), m. p. 117—120°, which gave as above *epi*euphol. Light petroleum proved less satisfactory for the chromatogram.

epiEuphyl Acetate.—*epi*Euphol (300 mg.), acetic anhydride (9 ml.), and pyridine (2 ml.) were heated at 100° for 4 hours. The solid product was dissolved in chloroform, and the solvent gradually replaced by methanol, from which *epieuphyl acetate* crystallised on cooling in highly refractive plates, m. p. 112—113°, $[\alpha]_D^{20}$ −66° (*c*, 0·95 in chloroform), unchanged by further crystallisation (Found: C, 82·0; H, 11·2. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

Dihydroepieuphol.—(*a*) *epi*Euphyl acetate (250 mg.) in ethyl acetate (12 ml.) and glacial acetic acid (3 ml.) was reduced in the presence of platinic oxide (30 mg.). Absorption of hydrogen (11·9 ml. at N.T.P. Calc. for $C_{32}H_{54}O_2$: 1 mol. = 11·2 ml.) was complete after 10 hours. The product crystallised from methanol in plates, m. p. 108—110°, showing no depression when mixed with *epi*euphyl acetate.

(*b*) *epi*Euphol (250 mg.) in ethanol (100 ml.) was hydrogenated in the presence of platinic oxide (300 mg.) at 80 atm. pressure for 6 hours. The product crystallised from methanol to give *dihydroepieuphol* as felted needles, m. p. 128—129°, $[\alpha]_D^{20}$ +33·9° (*c*, 0·73 in chloroform) (Found: C, 84·1; H, 12·0. $C_{30}H_{52}O$ requires C, 84·05; H, 12·2%). A mixture with *epi*euphol had m. p. 108—110°. Acetylation in the presence of pyridine and crystallisation of the product from methanol gave *dihydroepieuphyl acetate* as highly refractive plates, m. p. 111°, $[\alpha]_D^{20}$ −61·2° (*c*, 0·97 in chloroform) (Found: C, 81·8; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·55%). The m. p. of a mixture with *epi*euphyl acetate, m. p. 112—113°, was 108—110°.

Oxidation of epi*Euphol.*—epi*Euphol* (250 mg.) was heated with copper oxide (50 mg.) at 300° for 10 minutes in an atmosphere of carbon dioxide. The product was chromatographed through alumina (10 g.) with light petroleum to yield a solid which crystallised from ethanol as needles, m. p. 115—116°, showing no depression when mixed with euphone.

*Euphyl Toluene-*p*-sulphonate.*—Euphol (5 g., 1 mol.), pyridine (50 ml.), and toluene-*p*-sulphonyl chloride (5 g., 2 mols.) were allowed to react at 20° for 16 hours, and then poured into water. The ethereal extract, washed with dilute hydrochloric acid and dried, was chromatographed through alumina (30 g.). Crystallisation from acetone–water and twice from methanol gave *euphyl toluene-*p*-sulphonate* as felted needles, m. p. 103·5—104·5° (Found: C, 76·3; H, 9·7. $C_{37}H_{54}O_3S$ requires C, 76·5; H, 9·65%).

Euphatriene.—Euphyl toluene-*p*-sulphonate (5 g.), dry powdered calcium carbonate (6 g.), and pyridine (50 ml.) were refluxed for 2 hours under anhydrous conditions. The product was poured into water, and the ethereal extract, washed with acid, gave an oil. One chromatographic separation through alumina gave a solid which still contained a trace of sulphur. The product was hydrolysed with alcoholic potash and rechromatographed with ether as solvent. The oily solid was crystallised four times from acetone to give *euphatriene* as stout, long, colourless needles, m. p. 116—117°, $[\alpha]_D^{20}$ +115·8° (*c*, 1 in chloroform) (Found: C, 88·2; H, 11·8; Found, after sublimation: C, 88·3; H, 11·7. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%).

Euphene.—Euphatriene (300 mg.) in ethyl acetate–acetic acid (1 : 1; 250 ml.) was hydrogenated in the presence of Adams's catalyst. The product crystallised from acetone to give euphene as needles, m. p. 58—60°, $[\alpha]_D^{20}$ +37·6° (*c*, 1·03 in chloroform) (Found: C, 87·6; H, 12·4. Calc. for $C_{30}H_{52}$: C, 87·3; H, 12·7%), unchanged by hydrogenation under pressure. Roth and Jeger (*loc. cit.*) give m. p. 60·5—61°, $[\alpha]_D^{20}$ +34°.

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Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa. [*Received, October 18th,* 1949.]

140. *The* Senecio *Alkaloids. Part VI. The Isomerisation of Senecic Acid to* trans*-Senecic (Integerrinecic) Acid, and the General Structure of the "Necic" Acids.*

By Meyer Kropman and Frank L. Warren.

The lactone obtained from senecic acid is hydrolysed to give *trans*-senecic acid which is identical with integerrinecic acid, obtained by Manske by hydrolysis of integerrimine. The structural change is proved to involve geometrical isomerism.

The geometrical isomerism of senecic and integerrinecic acids parallels that found for isatinecic (*cis*-hydroxysenecic) and retronecic (*trans*-hydroxysenecic) acids. A general formula for these "necic" acids is advanced and represents a class of monoterpenes with a new irregular isoprene chain. The identity of integerrimine and squalidine is indicated.

The structure of senecic acid has been advanced previously by us (*J.*, 1949, 2852), and we have now prepared its geometrical isomeride. The lactone, m. p. 156°, obtained from senecic acid (cf. Richardson and Warren, *J.*, 1942, 452) was boiled with sodium hydroxide to open the lactone ring and then acidified to give trans-*senecic acid*, m. p. 150°. When this was mixed with a specimen of integerrinecic acid, m. p. 150°, kindly sent to us by Dr. R. H. F. Manske (*Canad. J. Res.*, 1939, **17**, 8) the melting-point was unchanged, but when it was mixed with senecic acid, m. p. 147°, the melting-point was depressed to 128°. The lactone obtained from *trans*-senecic acid was found to be identical with that from senecic acid. Since both acids give the same lactone and the *trans*-acid is regenerated from it the previously reported senecic acid lactone is actually *trans*-senecic (integerrinecic) acid lactone.

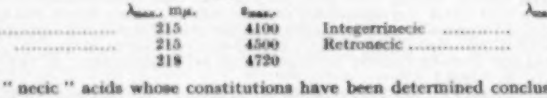
trans-Senecic acid was smoothly reduced catalytically to an oily acid which was converted into *bis-p-phenylphenacyl dihydrointegerrinecate*, m. p. 98°, which was identical with the bis-*p*-phenylphenacyl ester prepared from dihydrosenecic acid. The isomerism involved in the formation of integerrinecic acid must therefore involve the double bond. That the ethylenic linkage had not moved was proved by ozonolysis of *trans*-senecic acid, whereby acetaldehyde, identified as the octahydroxanthen derivative, was obtained.

Since senecic acid has the lower melting point and is the less stable form, senecic and integerrinecic acids are assigned *cis*- and *trans*-configurations, respectively, corresponding to isatinecic and retronecic acids (cf. Christie, Kropman, Novellie, and Warren, *J.*, 1949, 1703; Kropman and Warren, *loc. cit.*).

The ultra-violet extinction curve for *trans*-senecic acid showed a maximum in accordance with the αβ-unsaturated carboxylic grouping. The maxima observed for *cis*- (cf. Kropman and Warren, *loc. cit.*) and *trans*-senecic acid are of interest when compared with those for isatinecic and retronecic (*trans*-isatinecic) acids (cf. Christie, Kropman, Leisegang, and Warren, *J.*, 1949, 1700), and may be of significance in assigning geometrical configuration when only one form of other "necic" acids has been isolated:

	cis-Acids.			*trans*-Acids.	
	$\lambda_{max.}$ mμ.	$\varepsilon_{max.}$		$\lambda_{max.}$ mμ.	$\varepsilon_{max.}$
Senecic	215	4100	Integerrinecic	218	9333
Isatinecic	215	4500	Retronecic	218	9400
	218	4720			

The four "necic" acids whose constitutions have been determined conclusively may now be represented as *cis*- (I) and *trans*- (II) forms of a general formula with relationships as shown below.



(I.) (II.)

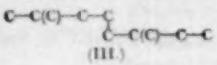
(Ia.) Senecic acid, m. p. 147°. (IIa). Integerrinecic acid, m. p. 150°.
(Ib.) Isatinecic acid, m. p. 148·5°. (IIb.) Retronecic acid, m. p. 181°.

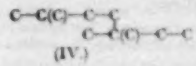
Where R = $CH_2X{\cdot}C(OH)(CO_2H){\cdot}CHMe{\cdot}CH_2{\cdot}$ (Ia and IIa; X = H). (Ib and IIb; X = OH).

Confirmation of this concept is afforded by the isolation by Konovalova and Danilova (*J. Gen. Chem. Russia*, 1948, **18**, 1198) of seneciphyllic acid, m. p. 144—145°, and *iso*seneciphyllic acid, m. p. 105—108°, by hydrolysis of seneciphylline with alcoholic and aqueous alkali, respectively. The two acids are reported as geometrical isomers and the *iso*-acid is the less stable form. On our nomenclature the *iso*-acid is *cis*-seneciphyllic acid (type I) and the seneciphyllic acid has the *trans*-configuration (type II). Therefore it is the *cis*-form in which the acid occurs in the alkaloid, and the *trans*-acid is formed by isomerisation with alcoholic

alkali or hydrochloric acid. The conditions which permit this isomerisation are those which effect lactone formation when this is possible. The isolation of the lactones of *trans*-senecic and retronecic acid from *cis*-senecic and isatinecic acid, respectively, is readily understood (cf. Christie, Kropman, Leisegang, and Warren, *loc. cit.*).

Schinz and Bourquin (*Helv. Chim. Acta*, 1946, **25**, 1599) formulated nine irregular, as contrasted with the regular (III), isoprene chains for the monoterpenes. Two only were known in Nature, namely (IV), represented by artemisia ketone, and (V), by lavandulol. The " necic " acids of known constitution represent a new class of monoterpenes with one (VI) of the remaining irregular chains.


(III.)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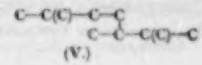
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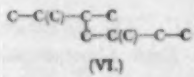
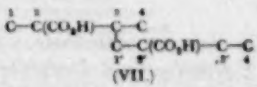

(VI.)


(VII.)

It is of significance that senecioic (2-methylprop-1-ene-1-carboxylic) acid possesses the *iso*pentane unit, and it is not improbable that all the " necic " acids possess the same carbon skeleton (VI). It may be of importance in considering biological synthesis that the two carboxylic groups appear in the butane units at the $C_{(1)}$ and $C_{(3')}$ atoms (VII) which are the positions normally occupied by methyl groups in the terpenes.

Manske (*loc. cit.*) found that integerrimine, $C_{18}H_{25}O_4N$, m. p. 172—172·5°, was hydrolysed to retronecine and integerrinecic acid, whilst Barger and Blackie (*J.*, 1939, 743) record that hydrolysis of squalidine, $C_{18}H_{25}O_4N$, m. p. 169°, gives retronecine and squalinecic acid. Squalinecic acid, m. p. 129°, was twice distilled, and was crystallised by inoculation with senecic acid but was not obtained pure. It contained three *C*-alkyl groups and the recorded analysis for carbon and hydrogen would indicate that " squalinecic " acid was a mixture of an acid, $C_{10}H_{14}O_3$, and its lactone, $C_{10}H_{14}O_4$. Furthermore a mixed melting-point determination on integerrinecic acid and its lactone carried out by us showed a melting point of 128°. It would seem to us that integerrimine is identical with squalidine, and in this connection it is of interest that both these alkaloids have only been found in small quantities associated with senecionine. A close relationship between *Senecio* alkaloids found together in the plant has been demonstrated previously (cf. Richardson and Warren, *J.*, 1943, 452; Christie *et al.*, *loc. cit.*).

Senecionine and integerrimine (squalidine) may now be formulated as *cis*- and *trans*-senecic esters of retronecine. Integerrimine is the first *Senecio* alkaloid in which the acid moiety has been found to occur in the *trans*-form, and may have been formed during isolation.

Experimental.

Micro-analyses by Drs. Weiler and Strauss, Oxford.

Senecic Acid.—Rosmarinine (7 g.), hydrated barium hydroxide (9·6 g.), and water (140 ml.) were heated under reflux for 1 hour. Carbon dioxide was passed through the hot solution, which was then filtered and the filtrate made acid to Congo-red with 5*N*-hydrochloric acid. Exhaustive extraction of the acid solution with ether gave the crude acid (4·2 g., 0·98 mol.) which, recrystallised from ethyl acetate, gave needles of senecic acid, m. p. 147° (uncorr.). *Bis-p-phenylphenacyl senecate* separated from ethanol as a white amorphous solid, m. p. 100—101° (Found: C, 75·3; H, 6·1. $C_{38}H_{34}O_6$ requires C, 75·5; H, 6·0%).

trans-*Senecic Acid.*—The lactone, m. p. 154° (Found: equiv., 194·4. Calc. for $C_{10}H_{14}O_4$: equiv., 198), (150 mg.) prepared from senecic acid, was heated for 1 hour on a water-bath with 2·5*N*-sodium hydroxide (10 ml.). On cooling, the solution was acidified to Congo-red with 5*N*-hydrochloric acid and extracted with ether. The ethereal solution gave a white solid which, after three crystallisations from water, gave trans-*senecic acid* as clusters of needles, m. p. 150°, $[\alpha]_D^{20}$ *ca.* +18° (*c*, 1·7 in ethanol) (Found: C, 55·9; H, 7·3%; equiv., 112·2. $C_{10}H_{14}O_3$ requires C, 55·6; H, 7·4%; equiv., 108). The melting point was undepressed when the *trans*-acid was mixed with integerrinecic acid whereas a mixture of senecic and *trans*-senecic acids had a melting point 128°. *Bis-p-phenylphenacyl* trans-*senecate* (*integerrinecate*) separated from ethanol as an amorphous white solid, m. p. 144—145° (Found: C, 75·0; H, 6·0. $C_{38}H_{34}O_6$ requires C, 75·5; H, 6·0%).

trans-*Senecic Acid Lactone.*—*trans*-Senecic acid (30 mg.) was treated several times with dilute hydrochloric acid and the hydrochloric acid evaporated each time. The product when recrystallised from ethyl acetate gave *trans*-senecic acid lactone, m. p. 152—154°, undepressed on admixture with the lactone from senecic acid.

Hydrogenation of Senecic and trans-*Senecic Acids.*—Senecic acid (168 mg.) was hydrogenated in the presence of platinic oxide to yield the oily dihydrosenecic acid. *Bis-p-phenylphenacyl dihydrosenecate* separated from ethanol as a white amorphous solid, m. p. 98° (Found: C, 74·9; H, 6·4. $C_{38}H_{36}O_6$ requires C, 75·3; H, 6·3%). Catalytic hydrogenation of *trans*-senecic acid (150 mg.) gave a colourless

oily acid which could not be induced to crystallise, and which gave a bis-*p*-phenylphenacyl ester, m. p. 98°, undepressed when mixed with the corresponding ester of dihydrosenecic acid.

Ozonolysis.—trans-Senecic acid (250 mg.) was dissolved in dry ethyl acetate and a stream of dry ozone passed through at 0° for ½ hour. The viscous, yellow, pungent osonide was treated with water and warmed in a stream of carbon dioxide. The issuing acetaldehyde was passed into water and treated with dimedon; a flocculent precipitate was obtained which, when heated under reflux with one drop of hydrochloric acid in 80% ethanol (4 ml.) and cooled, gave flat crystals, m. p. 175—176°, undepressed on mixing with the octahydroxanthen derivative of acetaldehyde.

The authors thank the South African Council for Scientific and Industrial Research for a bursary to one of them (M. K.) and a grant for equipment, and Mr. E. C. Leisegang of these laboratories for the determination of the extinction curves.

Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa. [*Received, November 7th,* 1949.]

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141. *The* Senecio *Alkaloids. Part VII. The Structure of Retrorsine and Isatidine: The Ester Groupings.*

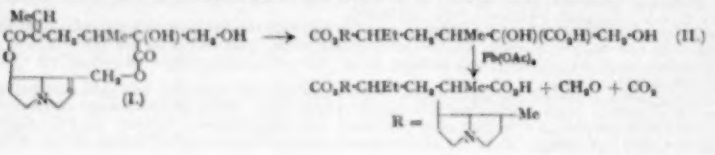
By Ernest C. Leisegang and Frank L. Warren.

Isatidine is reduced to retronecanyl dihydroisatinecate (dihydroretronecate) (II) which with lead tetra-acetate in aqueous acetic acid gives one mole of carbon dioxide. Thus in isatidine (retrorsine *N*-oxide) and retrorsine (I), the 2-carboxylic group of *cis*-1 : 2-dihydroxy-3-methylhept-5-ene-2 : 5-dicarboxylic acid (isatinecic acid) is esterified by the hydroxymethyl group of isatinecine and retronecine, respectively. The structure of similar *Senecio* alkaloids is indicated.

Isatidine is the ester of isatinecine, which Leisegang and Warren (*J.*, 1949, 486) showed to be retronecine *N*-oxide, with isatinecic acid, which Christie, Kropman, Novellie, and Warren (*J.*, 1949, 1703) gave as *cis*-1 : 2-dihydroxy-3-methylhept-5-ene-2 : 5-dicarboxylic acid. The general structure of isatidine is in conformity with de Waal's observation (*Onderstepoort J. Vet. Sci. Animal Husb.*, 1940, **14**, 445) that catalytic reduction gave octahydroanhydroisatidine, formulated as the dihydroisoatinecic (dihydroretronecic) ester of retronecanol by Christie, Kropman, Leisegang, and Warren (*J.*, 1949, 1700). We have now confirmed the structure of this reduction product by its hydrolysis to retronecanol, characterised as its picrate, and dihydroisatinecic acid, identified as its *p*-phenylphenacyl ester. Hydrogenolysis occurs at the carboxyl group esterified by the hydroxymethyl grouping of isatinecine.

To determine the orientation of the acid in isatidine we treated the reduced isatidine with lead tetra-acetate in acetic acid containing a small quantity of water. Carbon dioxide was immediately evolved as would be expected if the 2-carboxylic grouping were not esterified. The evolution of gas did not take place in anhydrous solvents; but the addition of a little water started the reaction so that the lead tetra-acetate caused fission of the glycol grouping to leave a keto-acid which was attacked by the reagent only in the presence of hydroxyl-forming compounds (cf. Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 1597). Since the quantity of carbon dioxide which dissolves in glacial acetic acid is large and varies considerably with the partial pressure of the gas (cf. Just, *Z. physikal. Chem.*, 1901, **37**, 342), the acetic acid was saturated and the reaction vessel filled with carbon dioxide before mixing the reagents. Only when the importance of this was pointed out by Dr. H. A. E. Mackenzie of these laboratories were we able to obtain quantitative yields of carbon dioxide. No evolution of gas was observed on treating either isatidine or retrosine with lead tetra-acetate under similar conditions.

The reduction of isatidine gave an oily product and hydrolysis of the alkaloid might have occurred during hydrogenation. Continuous ether extraction of the reduction product in hydrochloric acid gave, however, a negligible residue. On the other hand, previous hydrolysis of the reduced isatidine with barium hydroxide followed by continuous ether extraction of the acidified product for the same time gave an 80% yield of dihydroisatinecic acid:



These results lead to the structure of retronecanyl dihydroisatinecate (dihydroretronecate) (II) and hence to retrorsine (I) and isatidine, which Christie, Kropman, Leisegang, and Warren (*loc. cit.*) showed to be retrorsine *N*-oxide.

The "necine" bases so far investigated may be formulated as derivatives of retronecine, *e.g.* platynecine (dihydroretronecine) (Adams and Rogers, *J. Amer. Chem. Soc.*, 1941, **63**, 228) and rosmarinecine (hydroxydihydroretronecine) (Richardson and Warren, *J.*, 1942, 452). In view of the structural similarity of senecic and integerrinecic (*trans*-senecic) acids with isatinecic (hydroxysenecic) and retronecic (*trans*-hydroxysenecic) acids, respectively (Christie, Kropman, Novellie, and Warren, *loc. cit.*; Kropman and Warren, *J.*, 1949, 2852), the orientation of these acids in the complete alkaloids (shown below as derivatives of retronecine and senecic acid) is probably similar.

Senecionine [a]	= retronecine + senecic acid.
Integerrimine [b]	= retronecine + *trans*-senecic acid.
Platyphylline [c,d]	= dihydroretronecine + senecic acid.
Rosmarinine [d]	= hydroxydihydroretronecine + senecic acid.

[a] Barger and Blackie, *J.*, 1936, 743; [b] Manske, *Canad. J. Res.*, 1939, **17**, 1; [c] Orekhov and Tiedebel, *Ber.*, 1935, **68**, 650; with Konovalova, *ibid.*, 1186; [d] de Waal and Tiedt, *Onderstepoort J. Vet. Sci. Animal Husb.*, 1940, **15**, 251; Richardson and Warren (*loc. cit.*).

Experimental.

Retronecanyl Dihydroisatinecate (*Dihydroretronecate*).—Isatidine (4·70 g., 1 mol.) in 0·47*N*-sulphuric acid (50 ml., 4 mols.) and Adams's catalyst (130 mg.) were shaken with hydrogen at room temperature and 20 atmospheres pressure for 6 hours. The filtered solution was treated with just sufficient 0·4*N*-barium hydroxide to precipitate the sulphuric acid, and the filtered solution was evaporated under reduced pressure giving retronecanyl dihydroisatinecate as a clear oil which did not crystallise when kept. This product (1·01 g., 1 mol.) was boiled with barium hydroxide octahydrate (1·07 g., 1·2 mols.) in water (20 ml.) for ½ hour, cooled, acidified with hydrochloric acid, and extracted with ether for 6 hours. The ethereal extract gave dihydroisatinecic acid (530 mg., 0·8 mol.), which was characterised as its *p*-phenylphenacyl ester, m. p. 124—127°, undepressed when mixed with an authentic specimen (Christie *et al.*, *J.*, 1949, 1709). The aqueous solution gave retronecanyl picrate, m. p. 205—207° (Barger *et al.*, *J.*, 1935, 11, give m. p. 208°).

Retronecanyl dihydroisatinecate was acidified with hydrochloric acid and extracted under similar conditions. The ether extract gave a negligible residue.

Action of Lead Tetra-acetate on Retronecanyl Dihydroisatinecate.—Glacial acetic acid (10 ml.) was placed in a flask connected to a gas burette containing brine, and dry carbon dioxide swept through to saturate the acetic acid and to displace all the air. An excess of lead tetra-acetate was added and then retronecanyl dihydroisatinecate (280 mg., 1 mol.). No reaction was observed. Without opening the apparatus a small quantity of water was squirted into the mixture whereupon carbon dioxide was evolved (observed: 18·3 ml. at N.T.P. Calc. for $C_{11}H_{21}O_6N$: 18·7 ml.). Isatidine under similar conditions gave no carbon dioxide during 12 hours.

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Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa. [*Received, November 7th*, 1949.]

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142. *Some Heterocyclic N-Oxides.*

By P. Mamalis and V. Petrow.

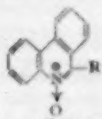
Although the preparation of some *phenanthridine N-oxides* has been accomplished, attempts to obtain the "*N*-oxide" analogue of Dimidium bromide (II) have proved unsuccessful.

By the action of phosphorus oxychloride on *9-phenylphenanthridine N-oxide*, *3-chloro-9-phenylphenanthridine* has been obtained. *9-Methylphenanthridine N-oxide* similarly gave 9-chloromethylphenanthridine together with what was probably a *3-chloro-9-methylphenanthridine*.

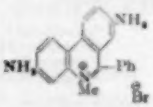
In 1941 McIlwain (*Nature*, **148**, 628) reported that iodinin, the pigment of *Chromobacterium iodinum*, showed marked antibacterial action on a number of organisms. Chemical work on its structure revealed that the compound was a dihydroxyphenazine di-*N*-oxide, a result which led McIlwain (*J.*, 1943, 322) to the synthesis of a number of phenazine and quinoxaline di-*N*-oxides which showed varying degrees of antibacterial action. In 1943 White and Hill (*J. Bact.*, 1943, **45**, 433) reported the isolation of the antibiotic "aspergillic acid" which possessed an antibacterial range greater than that of penicillin (see Glister, *Nature*, 1941, **148**, 470) and

proved to be a hydroxypyrazine *N*-oxide (see Newbold and Spring, *J.*, 1947, 372). The existence of *N*-oxide residues in at least two naturally occuring antibacterial agents appeared significant, particularly as the corresponding " deoxido "-compounds were without biological interest. We therefore undertook the preparation of some phenanthridine *N*-oxides (Ia) for study as antibacterial agents and, as *N*-oxides bear an electronic resemblance to quaternary salt (*e.g.*, II), for examination as trypanocides. In particular, we wished to prepare the " *N*-oxide " analogue of the effective trypanocide, Dimidium bromide (II) (see Walls, *J.*, 1945, 294). Some new *quinoline* and *quinoxaline* N-*oxides* were also prepared, as we required a range of compounds which could function as mild oxidising agents for chemotherapeutic studies employing the anaerobic organism *Entamoeba histolytica*.

(I.)



(Ia.)



(II.)

Conversion of phenanthridine itself, and of its 9-methyl and 9-ethyl derivatives, into the corresponding N-*oxides* was smoothly achieved by employing perphthalic acid. Peracetic acid, however, proved to be the reagent of choice for the preparation of the 9-arylphenanthridine *N*-oxides, which generally differed from their 9-alkyl analogues in failing to liberate iodine from potassium iodide under the experimental conditions specified by McIlwain (*J.*, 1943, 342) for this test.

The mononitrophenylphenanthridines were converted into their N-*oxides* with somewhat greater difficulty and required longer reaction periods with peracetic acid. This result is probably due to the electron-attracting effect of the nitro-group on the free electron pair present on the ring nitrogen and available for oxide formation. Similar difficulties were experienced with the dinitrophenylphenanthridines. Although 3-*nitro*-9-p-*nitrophenylphenanthridine* N-*oxide* was obtained from the corresponding dinitro-compound in low yield, all attempts to prepare 2 : 7-dinitro-9-phenylphenanthridine *N*-oxide for conversion into the Dimidium bromide analogue were unsuccessful.

Reduction of the nitro-9-phenylphenanthridine *N*-oxides with stannous chloride in hydrochloric acid solution furnished the corresponding *amino*-9-*phenylphenanthridine* N-*oxides*. Reduction of 3-nitro-9-*p*-nitrophenylphenanthridine *N*-oxide, on the other hand, invariably resulted in loss of the oxido-grouping and formation of 3-amino-9-*p*-aminophenylphenanthridine. Limited success attended efforts at the direct oxidation of 3-*diacetylamino*-9-p-*diacetylaminophenylphenanthridine*, wherein the corresponding N-*oxide* was obtained in very low yield. Attempts to extend this reaction to 7-*diacetylamino*-9-p-*diacetylaminophenyl*-, 2 : 7-*bisdiacetylamino*-9-*phenyl*-, and 2 : 7-dicarbethoxyamino-9-phenyl-phenanthridine proved unsuccessful, however, and further work on the " *N*-oxide " analogue of Dimidium bromide (II) was abandoned.

9-4′-*Pyridylphenanthridine*, prepared by ring closure of 2 : 4′-*picolinamidodiphenyl*, formed a homogeneous *monoxide* on treatment with 1·1 equivalents of perphthalic acid. The constitution of a 9-4′-*pyridylphenanthridine* 1′-*oxide* has been assigned to this compound from analogy with related work on the monoquaternation of 9-3′-pyridylphenanthridine (Petrow and Wragg, *J.*, 1947, 1410) and on general theoretical grounds. Reaction with excess of perphthalic acid led to the formation of the corresponding *dioxide*. Attempts to convert 9-(5-*nitro*-2-*furyl*)*phenanthridine* into its oxide were unsuccessful.

The reaction of phenanthridine *N*-oxide with phosphorus oxychloride followed the pattern established for similar compounds (see, *e.g.*, Baxter, Newbold, and Spring, *J.*, 1948, 1859), 9-chlorophenanthridine being formed. When 9-phenylphenanthridine *N*-oxide was treated in the same way, however, a *chloro*-9-*phenylphenanthridine* was obtained, identical with authentic 3-*chloro*-9-*phenylphenanthridine* prepared by the Sandmeyer reaction from the corresponding amino-compound. When 9-methylphenanthridine *N*-oxide was treated with phosphorus oxychloride, two halogenated products were obtained. One of these was identified with 9-chloromethylphenanthridine previously described by Morgan and Walls (*J.*, 1931, 2447). The other product has, by analogy with its phenyl analogue, been assigned the constitution of a 3-*chloro*-9-*methylphenanthridine*.

Experimental.

(M. p.s are uncorrected. Microanalyses are by the Analytical Department, The British Drug Houses Ltd., and by Drs. Weiler and Strauss, Oxford.)

Substituted 2-Benzamidodiphenyls.—The acid chloride (0·1 mol.) (prepared from the acid and thionyl chloride) was added in portions to a solution of 2-aminodiphenyl (0·1 mol.) in pyridine (15—20 ml.), and the mixture heated on the steam-bath for 2 hours to complete the reaction. Addition of dilute hydrochloric acid usually precipitated the amide as a solid, which was collected, washed, and crystallised from alcohol or alcohol–light petroleum. Occasionally, preliminary vacuum-distillation was required before the amide could be obtained as a solid. The compounds listed in Table I were thus prepared. The yields are based on the acid used.

5-Carbethoxyamino-2-acetamidodiphenyl, prepared by reduction of 5-nitro-2-acetamidodiphenyl followed by carbethoxylation, formed small pale-cream needles, m. p. 127—128° (77%) (Found: C, 68·4; H, 6·0. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1%), from benzene–light petroleum.

4'-Carbethoxy-2-acetamidodiphenyl, prepared as for the foregoing compound, formed (91%) silvery leaflets, m. p. 160—161° (cf. Walls, *J.*, 1947, 67).

2-Nitro-4 : 4'-dibenzamidodiphenyl.—2-Nitrobenzidine (23·6 g.) in warm pyridine (30 ml.) was treated with benzoyl chloride (30 g.) in portions. After 30 minutes on the water-bath the *product* was isolated and purified from pyridine–light petroleum, to give pale yellow prisms, m. p. 290—291° (Found: C, 71·7; H, 4·5. $C_{26}H_{19}O_4N_3$ requires C, 71·4; H, 4·4%), in nearly quantitative yield.

2-Amino-4 : 4'-dibenzamidodiphenyl.—Finely powdered 2-nitro-4 : 4'-dibenzamidodiphenyl (10·7 g.) was stirred with concentrated hydrochloric acid (83 ml.) containing a little alcohol to prevent frothing, and a solution of stannous chloride (47 g.) in concentrated hydrochloric acid (50 ml.) added. After 2 hours on the water-bath the mixture was poured, with stirring, into excess of sodium hydroxide solution (30%), and the precipitated solids extracted with boiling pyridine. Evaporation of the extract under reduced pressure, followed by crystallisation of the residue (12·0 g.; m. p. 255—258°) from aqueous pyridine, gave *2-amino-4 : 4'-dibenzamidodiphenyl*, buff-coloured prisms, m. p 270° (Found: C, 76·9; H, 5·2. $C_{26}H_{21}O_2N_3$ requires C, 76·7; H, 5·2%).

4 : 4'-Dicarbethoxyamino-2-dimethylaminodiphenyl.—A well-stirred solution of 2-amino-4 : 4'-dicarbethoxyaminodiphenyl (13 g.) in water (50 ml.) at 80° was treated in portions with aqueous sodium hydroxide (19 g. in 28 ml. of water) and methyl sulphate (35 g.), added alternately so that the mixture remained alkaline. After a further 30 minutes' heating, the product was collected, heated with acetic anhydride (20 ml.) for 10 minutes on the water-bath, and poured into dilute sulphuric acid (20 ml. acid in 300 ml. of water), and the mixture was filtered while hot. The filtrate was made alkaline, giving *4 : 4'-dicarbethoxyamino-2-dimethylaminodiphenyl*, prismatic needles (6·7 g.), m. p. 171—172° (Found: C, 63·7; H, 7·5. $C_{20}H_{24}O_4N_2,C_6H_6O$ requires C, 63·3; H, 7·5%), from ethanol.

2-Benzamido-4'-chlorosulphonyldiphenyl.—2-Benzamidodiphenyl (21·2 g.) was added in portions with stirring to chlorosulphonic acid (42·4 g.) at 10°. The mixture was then heated at 60° for 2 hours and, after cooling, poured on ice. The sticky product was dissolved in chloroform and precipitated with light petroleum, giving *2-benzamido-4'-chlorosulphonyldiphenyl*, needles (12·2 g.), m. p. 162—163° (Found: C, 62·1; H, 3·9; Cl, 9·9. $C_{19}H_{14}O_3ClNS$ requires C, 61·4; H, 3·8; Cl, 9·5%), from benzene (cf. B.PP. 597,809, 597,810 for orientation).

2-Benzamido-4'-2''-pyridylsulphamyldiphenyl, prepared from the above compound, formed prisms m. p. 223°, from ethoxyethyl alcohol (Found: C, 66·5; H, 4·8. $C_{24}H_{19}O_3N_3S$ requires C, 67·1; H, 4·5%). The *p-chlorophenylsulphamyl* derivative separated from ethoxyethyl alcohol in small leaflets, m. p. 239° (Found: C, 64·9; H, 4·5. $C_{25}H_{18}O_3N_2SCl$ requires C, 64·9; H, 4·1%). The *sulphonemorpholide* formed needles, m. p. 161—163° (Found: C, 65·3; H, 5·3. $C_{23}H_{23}O_4N_3S$ requires C, 65·4; H, 5·3%), from aqueous ethoxyethyl alcohol. The *sulphonopiperidide* formed needles, m. p. 102—104° (Found: N, 6·6. $C_{24}H_{25}O_3N_3S$ requires N, 6·7%), from ethanol.

The *p-nitrophenylsulphamyl* derivative formed pale yellow leaflets, m. p. 247° (Found: C, 63·3; H, 3·8. $C_{25}H_{18}O_5N_3S$ requires C, 63·4; H, 4·0%), from ethoxyethyl alcohol.

2-iso-Nicotinamidodiphenyl.—*iso*Nicotinic acid (30 g.), prepared (56% yield) by the method of Linnell and Vyas (*Quart. J. Pharm.*, 1947, **20**, 120), was heated under reflux with thionyl chloride (85 ml.) for 6 hours. Unchanged thionyl chloride was removed under reduced pressure, and the residue evaporated with benzene. The *iso*nicotinoyl chloride hydrochloride in gently refluxing chlorobenzene (320 ml.) was treated in portions with 2-aminodiphenyl (40 g.) in chlorobenzene (85 ml.). Heating was continued for a further 30 minutes, and the mixture was cooled, the chlorobenzene decanted off, and the semi-solid residue washed by decantation with ether. The product was dissolved in hot methyl alcohol (*ca.* 400 ml.), the base (42·5 g.; m. p. 107—111°) precipitated with aqueous ammonia, and the mixture cooled. 2-iso*Nicotinamidodiphenyl* formed needles, m. p. 113·5° (Found: C, 79·0; H, 5·3. $C_{18}H_{14}ON_2$ requires C, 78·8; H, 5·1%), from aqueous methanol.

The compounds listed in Table II were prepared in a similar way.

4'-Chloro-2-benzamidodiphenyl.—The method of Bradshaw and Wilson (*J. Amer. Chem. Soc.*, 1946, **68**, 405) was modified as follows: 4'-Chloro-2-nitrodiphenyl (11·2 g.), ethanol (45 ml.), water (12 ml.), reduced iron (15 g.), and a few drops of concentrated hydrochloric acid were heated under reflux on the water-bath for 1 hour. The mixture was then made just alkaline with aqueous ammonia and filtered hot. Extraction of the solids with hot ethanol gave an oil from which 4'-chloro-2-benzamidodiphenyl was obtained, on benzoylation, as needles (10·6 g.), m. p. 167—169°, from ethanol.

5-Chloro-2-acetamidodiphenyl.—The following improved method was used: 2-acetamidodiphenyl (10·6 g.) and fused sodium acetate (12·3 g.) in glacial acetic acid (45 ml.) on the water-bath were treated with a stream of chlorine until 3·5 g. had been absorbed. Heating was continued for a further 30 minutes and the mixture was then diluted with water and extracted with chloroform. The product was distilled under reduced pressure, the fraction, b. p. 170—200°/0·05 mm., yielding 5-chloro-2-acetamidodiphenyl, m. p. 120—121° (Found: C, 68·9; H, 5·0. Calc. for $C_{14}H_{12}ONCl$: C, 68·4; H, 4·9%), on crystallisation from alcohol–light petroleum (cf. Scarborough and Waters, *J.*, 1927, 93).

TABLE I.

Substituted diphenyls.

Substituent.	M. p. or b. p.	Yield, %	Formula.	Found, %. C.	H.	N.	Reqd., %. C.	H.	N.	Description.*
2-o-*Methylbenzamido*-	88—89°	52	$C_{20}H_{17}ON$	83·1	5·6	—	83·4	6·0	—	Needles
2-m-*Methylbenzamido*-	b. p. 185 (0·05 mm.) 89—90	63	,,	83·5	6·0	—	83·4	6·0	—	Needles
2-p-*Methylbenzamido*-	b. p. 180 (0·08 mm.) 107—108	66	,,	83·9	5·8	4·7	83·4	6·0	4·9	Needles
2-o-*Chlorobenzamido*-	103	58	$C_{19}H_{14}ONCl$	73·9	4·5	°	74·2	4·3	°	Needles[b]
2-m-*Chlorobenzamido*-	107—108	67	,,	74·2	4·6	—	74·2	4·3	—	Wispy needles
2-p-*Chlorobenzamido*-	104	64	,,	73·6	4·5	—	74·2	4·3	—	Wispy needles
5-*Nitro*-2-*benzamido*-	148—149	80	$C_{19}H_{14}O_3N_2$	71·1	4·3	—	71·7	4·4	—	Flat yellow needles[b]
2-o-*Anisamido*-	162	40	$C_{20}H_{17}O_2N$	79·1	5·6	—	79·2	5·7	—	Flat needles[c]
2-m-*Anisamido*-	76—77	58	,,	79·2	5·7	—	79·2	5·7	—	Needles[a]
2-(2 : 5-*Dimethoxybenzamido*)-	134—135	68	$C_{21}H_{19}O_3N$	75·8	5·6	—	75·7	5·8	—	Leaflets
2-(3 : 4-*Dimethoxybenzamido*)-	128—130	73	,,	76·0	5·8	4·1	75·7	5·8	4·2	Small needles[c]
2-p-iso*Propoxybenzamido*-	150 (softens 115)	69	$C_{23}H_{21}O_2N$	79·8	6·4	—	79·7	6·4	—	Wispy needles[c]
2-(p-n-*Propoxybenzamido*)-	116—118	49	,,	79·6	6·5	—	79·7	6·4	—	Long needles
2-(3-*Methoxy*-4-*ethoxybenzamido*)-	111 b. p. 223 (0·07 mm.)	58	$C_{23}H_{21}O_3N$	76·2	6·3	—	76·1	6·1	—	Needles
2-(3-*Methoxy*-4-*isopropoxybenzamido*)-	148·5	73	$C_{24}H_{23}O_3N$	—	—	3·9	—	—	3·9	Needles
2-(3 : 4-*Methylenedioxybenzamido*)-	145—146	66	$C_{20}H_{13}O_4N$	75·6	4·7	—	75·7	4·8	—	Needles
2 : 4 : 4′-*Tribenzamido*-	285	59	$C_{33}H_{25}O_3N_3$	77·2	4·5	—	77·5	4·9	—	Micro-prisms[c]
2-2′-*Furamido*-	76—77·5	71	$C_{17}H_{12}O_3N$	77·0	5·2	—	77·6	5·0	—	Needles
2-(5-*Nitro*-2-*furamido*)-	134—135	55	$C_{17}H_{12}O_4N_2$	65·7	4·1	—	66·2	3·9	—	Yellow leaflets
4′-*Carbethoxyamino*-2-(5-*nitro*-2-*furamido*)-	179—180	50	$C_{20}H_{17}O_6N_3$	60·8	4·4	—	60·8	4·3	—	Flat needles[b]

* Recrystallised from: [a] light petroleum, [b] ethoxyethyl alcohol, [c] benzene, [d] pyridine. [e] Found: Cl, 11·4. Reqd.: Cl, 11·6%.

TABLE II.

Substituted diphenyls.

Subtituent.	M. p.	Yield, %.	Formula.	Found, %. C.	H.	N.	Reqd., %. C.	H.	N.	Description.*
2-*Picolinamido*-	100°	82	$C_{19}H_{16}ON_2$	78·2	5·3	—	78·8	5·1	—	Large buff needles[a]
4′-*Nitro*-2-*picolinamido*-	215—217	75	$C_{19}H_{15}O_3N_3$	67·3	4·0	—	67·7	4·1	—	Wispy yellow needles[b]
4′-*Nitro*-2-*isonicotinamido*-	185—186	85	,,	67·1	4·1	—	67·7	4·1	—	Wispy yellow needles[a]
5-*Nitro*-2-*picolinamido*-	207—208	61	,,	67·8	4·1	—	67·7	4·1	—	Needles[b]
5-*Nitro*-2-*isonicotinamido*-	138	63	,,	67·8	4·1	—	67·7	4·1	—	Buff prisms[d]
4′-*Carbethoxyamino*-2-*picolinamido*-	181—182 (softens 158)	68	$C_{21}H_{19}O_3N_3,C_6H_6$	73·0	5·6	—	73·8	5·7	—	Needles[a]
2-(2-*Phenyl*-4-*quinolylamido*)-	173	76	$C_{32}H_{20}ON_2$	81·9	4·9	6·8	81·9	5·0	6·9	Prisms[f]
5-*Nitro*-2-(2-*phenyl*-4-*quinolylamido*)-	228	72	$C_{32}H_{19}O_3N_3$	75·1	4·5	—	75·5	4·3	—	Prisms[g]
4′-*Nitro*-2-(2-*phenyl*-4-*quinolylamido*)-	223	83	,,	75·5	4·5	—	75·4	4·3	—	Small needles[b]
4′-*Carbethoxyamino*-2-(2-*phenyl*-4-*quinolylamido*)-	195	81	$C_{35}H_{28}O_3N_3$	76·2	4·9	—	76·4	5·2	—	Flat buff needles[c]
2-(2-o-*Chlorophenyl*-5 : 6-*benz*-4-*quinolylamido*)-	234—236	70	$C_{32}H_{21}ONCl$	79·0	4·7	—	79·3	4·4	—	Cream needles[b]

* Recrystallised from: [a] light petroleum, [b] ethoxyethyl alcohol, [c] methanol, [d] benzene–light petroleum, [e] benzene, [f] acetone, [g] nitrobenzene–ether, [h] nitrobenzene.

2-(p-*Aminobenzamido*)*diphenyl*, prepared by reduction of the corresponding nitro-compound with reduced iron, separated (87%) from ethanol in cubes, m. p. 144—145° (Found: C, 79·3; H, 5·7; N, 9·5. $C_{19}H_{16}ON_2$ requires C, 79·1; H, 5·6; N, 9·7%). It was converted into 2-(p-*carbethoxyaminobenzamido*)-*diphenyl*, needles, m. p. 166—167° (Found: C, 73·7; H, 6·0. $C_{23}H_{20}O_3N_2$ requires C, 73·3; H, 5·6%), from ethanol, by the method of Leslie and Turner (*J.*, 1943, 1588).

9-*Substituted Phenanthridines.*—The amidodiphenyl (1 part), phosphorus oxychloride (2 parts), and nitrobenzene (3 parts) were heated under reflux in an oil-bath for 1½—2½ hours. The reaction mixture was poured on excess of ice–sodium hydroxide solution, and the nitrobenzene removed in steam. After cooling, the separated solids were collected, washed, and purified by crystallisation. The compounds listed in Table III were thus prepared.

9-4′-*Pyridylphenanthridine dihydrochloride* formed yellow prisms, m. p. 235° (decomp.) (Found: C, 65·3; H, 4·4. $C_{18}H_{12}N_2,2HCl$ requires C, 65·7; H, 4·3%), from ethanol.

3-*Chloro*-9-*phenylphenanthridine.*—3-Amino-9-phenylphenanthridine (5·0 g.), dissolved in concentrated hydrochloric acid (7 ml.) and water (3 ml.), was diazotised at 0° with sodium nitrite (1·4 g.) dissolved in a little water. The diazonium solution was then rapidly added to cuprous chloride solution [prepared from cupric sulphate (6·2 g.), sodium chloride (1·75 g.), and water (20 ml.; saturated with SO_2), the resulting cuprous chloride being dissolved in hydrochloric acid (12 ml.)]. After being kept overnight, the precipitated solids were collected and extracted with sodium hydroxide solution, and the insoluble residue was crystallised from ethanol. 3-*Chloro*-9-*phenylphenanthridine* formed yellow leaflets (1·3 g.), m. p. 141—142° (Found: C, 79·0; H, 4·4. $C_{19}H_{12}NCl$ requires C, 78·7; H, 4·3%).

7-*Amino*-9-*phenylphenanthridine.*—Finely powdered 7-nitro-9-phenylphenanthridine (14·5 g.) was stirred with concentrated hydrochloric acid (60 ml.) while a solution of stannous chloride (40 g.) in hydrochloric acid (43 ml.) was added. After 3 hours on the water-bath the cooled mixture was filtered, the yellow stannichloride dissolved in water, and the solution basified. Hot ethoxyethyl alcohol extracted 7-*amino*-9-*phenylphenanthridine*, yellow needles (10·8 g.), m. p. 168° (Found: C, 83·8; H, 5·3. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2%), from ethanol.

3-*Amino*-9-m-*aminophenylphenanthridine*, prepared similarly to the foregoing compound, formed yellow prisms (63%), m. p. 201° (Found: C, 79·5; H, 5·1. $C_{19}H_{15}N_3$ requires C, 80·0; H, 5·3%), from ethanol.

7-*Amino*-9-m-*aminophenylphenanthridine*, prepared similarly to the above compound, formed yellow prismatic needles (64%), m. p. 210° (Found: C, 79·4; H, 5·2. $C_{19}H_{15}N_3$ requires C, 80·0; H, 5·3%), from ethoxyethyl alcohol. The NN′-*diacetyl* derivative formed needles, m. p. >290° (Found: C, 74·5; H, 5·0; N, 11·1. $C_{23}H_{19}O_2N_3$ requires C, 75·2; H, 4·7; N, 11·4%), from alcohol.

5-*Amino*-9-*phenylphenanthridine*, prepared by ring closure of 2 : 2′-dibenzamidodiphenyl (3 g.) with phosphorus oxychloride (6 g.) and nitrobenzene (9 ml.) at 160° for 2 hours, formed yellow prisms, m. p. 164° (Found: C, 84·1; H, 5·3; N, 10·4. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%), from aqueous ethanol. The *monohydrochloride* formed yellow needles, m. p. 335—338° (decomp.) (Found: C, 74·3; H, 4·9; N, 8·6. $C_{19}H_{14}N_2,HCl$ requires C, 74·4; H, 4·9; N, 9·1%), from aqueous alcohol.

9-p-*Diacetylaminophenylphenanthridine.*—9-*p*-Aminophenylphenanthridine (5 g.), acetic anhydride (50 ml.), and one drop of concentrated sulphuric acid were heated under reflux for 4 hours. Excess of acetic anhydride was removed under reduced pressure leaving 9-p-*diacetylaminophenylphenanthridine*, m. p. 207° (Found: C, 78·4; H, 5·3. $C_{23}H_{18}O_2N_2$ requires C, 77·9; H, 5·1%) after crystallisation.

3-*Diacetylamino*-9-p-*diacetylaminophenylphenanthridine* crystallised from ethoxyethyl alcohol–ethanol (1 : 2) in needles, m. p. 221—222° (softening at 217°) (Found: C, 71·0; H, 5·3. $C_{27}H_{23}O_4N_3$ requires C, 71·5; H, 5·1%).

7-*Diacetylamino*-9-p-*diacetylaminophenylphenanthridine* formed small prisms, m. p. 227—229° (Found: C, 71·0; H, 5·1. $C_{27}H_{23}O_4N_3$ requires C, 71·5; H, 5·1%), from aqueous ethanol.

3-*Carbethoxyamino*-9-*methylphenanthridine*, pale yellow prisms (3 g.) from benzene, m. p. 177—179° (Found: C, 72·7; H, 5·8. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·8%), was obtained by ring closure of 5-carbethoxy-2-acetamidodiphenyl (5·0 g.) with phosphorus oxychloride (10 ml.) under reflux for 45 minutes.

9-p-*Hydroxyphenylphenanthridine.*—9-*p*-Aminophenylphenanthridine (2·0 g.) in 2*N*-sulphuric acid (20 ml.) was heated on the water-bath and then cooled to 0°. Sodium nitrite (0·8 g.), dissolved in a little water, was then added, and the diazotised solution poured into water (50 ml.) at 70°. After being kept overnight, the solids were collected, purified by solution in alkali, and crystallised from ethanol. 9-p-*Hydroxyphenylphenanthridine* formed prismatic needles (1·4 g.), m. p. 237° (Found: C, 83·7; H, 4·8. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%).

9-m-*Hydroxyphenylphenanthridine*, prepared similarly, formed buff-coloured microneedles, m. p. 225—226° (Found: C, 83·7; H, 4·8. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%), from aqueous ethanol.

9-*Morpholinomethylphenanthridine.*—9-Chloromethylphenanthridine (6·3 g.), morpholine (8·5 g.), alcohol (25 ml.), and chloroform (5 ml.) were heated under reflux for 2 hours. Water was added, the mixture extracted with chloroform and concentrated to small bulk, and light petroleum added. 9-*Morpholinomethylphenanthridine* separated and was obtained as yellow prisms, m. p. 95° (Found: C, 77·6; H, 6·7. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5%), from light petroleum.

9-(5-*Nitro*-2-*furyl*)*phenanthridine*, yellow needles, m. p. 187° (Found: C, 69·6; H, 3·5. $C_{17}H_{10}O_3N_2$ requires C, 70·3; H, 3·5%), from acetone, was obtained (36%) by heating 2-(5-nitro-2-furamido)-diphenyl (5·0 g.) with phosphorus oxychloride (10 ml.) and nitrobenzene (15 ml.) for 30 minutes at 160°.

9-p-*Diguanidophenylphenanthridine.*—9-*p*-Aminophenylphenanthridine (2·65 g.), dicyandiamide (2·7 g.), water (15 c.c.), and hydrochloric acid (1 c.c.) were heated under reflux for 3 hours. The mixture was basified with ammonia, and the solid collected and crystallised from ethanol, from which it separated as needles (1·0 g.) (Found, in a sample dried at 100°/30 mm.: C, 69·2; H, 5·2; N, 23·0. $C_{21}H_{19}N_9,\frac{1}{2}H_2O$ requires C, 69·4; H, 5·3; N, 23·1%).

7-*Diguanido*-9-*phenylphenanthridine monohydrate*, similarly prepared, formed prismatic needles, m. p. 153° (decomp.) (Found: C, 68·0; H, 5·7; N, 22·4. $C_{21}H_{19}N_9,H_2O$ requires C, 67·7; H, 5·4; N, 22·5%), from alcohol. The *picrate* formed small yellow prisms, m. p. 235° (decomp.) (Found: N, 20·6. $C_{21}H_{19}N_9,C_6H_3O_7N_3$ requires N, 21·6%), from ethoxyethyl alcohol.

TABLE III.

9-Substituted phenanthridines.

Substituent.	M. p.	Yield, %	Formula.	Found, %. C.	H.	N.	Reqd., %. C.	H.	N.	Description. [a]
m-Tolyl-	98—99°	78	$C_{20}H_{15}N$	89·6	5·9	—	89·2	5·6	—	Prismatic needles [c]
p-Tolyl-	108	73	,,	88·8	5·6	—	89·2	5·6	—	Needles [c, (1)]
7-Chloro-9-phenyl-	120	57	$C_{19}H_{12}NCl$	78·6	4·3	—	78·7	4·3	—	Cream needles [b]
o-Chlorophenyl-	125	94	,,	78·5	4·0	—	78·7	4·3	—	Prisms [b]
m-Chlorophenyl-	137—138	87	,,	78·5	4·1	—	78·7	4·3	—	Silver needles [c]
p-Chlorophenyl-	157·5	84	,,	79·2	4·2	—	78·7	4·3	—	Silver needles [b]
3-Nitro-9-phenyl-	228—229	96	$C_{19}H_{12}O_2N_2$	75·5	4·0	—	76·0	4·0	—	Pale yellow wispy needles [d, (2)]
2 : 7-Dibenzamido-9-phenyl-	321—322	89	$C_{33}H_{23}O_2N_3$	79·6	4·8	8·1	80·3	4·7	8·5	Pale cream micro-needles [a, (2)]
o-Methoxyphenyl-	127	75	$C_{20}H_{15}ON$	84·2	5·3	5·0	84·2	5·3	4·9	Needles [f]
m-Methoxyphenyl-	128—129	89	,,	84·2	5·3	—	84·2	5·3	—	Prisms [f]
p-Methoxyphenyl-	146	80	,,	83·7	4·8	—	84·2	5·3	—	Needles [f]
2'-Methoxy-5'-bromophenyl-	148	77	$C_{20}H_{14}ONBr$	65·8	3·9	—	66·0	3·9	—	Cubes [f]
p-Ethoxyphenyl-	149—150	64	$C_{21}H_{17}ON$	84·0	5·9	4·8	84·2	5·7	4·7	Flat needles [f]
2' : 5'-Dimethoxyphenyl-	163	95	$C_{21}H_{17}O_2N$	80·0	5·4	—	80·0	5·4	—	Prisms [f]
3' : 4'-Dimethoxyphenyl-	169	88	,,	79·6	5·3	—	80·0	5·4	—	Prismatic needles [f]
3' : 4'-Methylenedioxyphenyl-	113	70	$C_{20}H_{13}O_2N$	79·8	4·4	4·3	80·4	4·4	4·7	Needles [f]
p-n-Propoxyphenyl-	116—117	96	$C_{23}H_{17}O_2N$	—	—	4·1	—	—	4·5	Cream needles [f]
p-iso Propoxyphenyl-	118—119	62	,,	91·0	5·8	—	90·3	6·1	—	Needles [f]
3'-Methoxy-4'-ethoxyphenyl-	118—120	53	$C_{22}H_{19}O_2N$	—	—	4·7	—	—	4·3	Needles [f]
3'-Methoxy-4'-isopropoxyphenyl-	137—139	86	$C_{23}H_{21}O_2N$	80·4	5·8	—	80·4	6·2	—	Needles [f]
3'-Methoxy-4'-n-propoxyphenyl-	128—129	77	,,	79·8	6·2	—	80·4	6·2	—	Needles [f]
4'-Pyridyl-	160	74	$C_{18}H_{12}N_2$	84·2	4·8	—	84·4	4·7	—	Prismatic needles [a, (4)]
4'-Pyridyl- dihydrochloride	235 (decomp.)	—	$C_{18}H_{12}N_2,2HCl$	65·3	4·4	—	65·7	4·3	—	Yellow prisms [f]
2'-Phenyl-4'-quinolyl-	183—184	63	$C_{28}H_{18}N_2$	87·5	4·8	—	87·9	4·7	—	Pale cream prisms [f, (3)]
3-Nitro-9-(2-phenyl-4-quinolyl)-	>295	70	$C_{28}H_{17}O_2N_3$	79·0	4·1	—	78·7	4·0	—	Small needles [d, (3)]
7-Nitro-9-(2-phenyl-4-quinolyl)-	282	58	$C_{28}H_{17}O_2N_3$	78·2	3·8	—	78·7	4·0	—	Pale yellow needles [d, (3)]
9-(2-o-Chlorophenyl-5 : 6-benz-4-quinolyl-)	260	65	$C_{32}H_{18}NCl$	82·3	4·1	6·0	81·6	3·9	5·3	Leaflets [b]

(1) Since completion of this preparation Gilman and Nelson (*J. Amer. Chem. Soc.*, 1948, **70**, 3316) have described an alternative preparation from phenanthridine and tolyl-lithium.

Periods of refluxing: (2) 16 hours, (3) 3½ hours, (4) 16 hours, (5) 18 hours.

[a] Recrystallised from: [a] light petroleum, [b] methanol, [c] acetone, [d] nitrobenzene, [e] aq. pyridine, [f] ethanol, [g] acetone–ethanol, [h] ethoxyethyl alcohol.

Phenanthridine 10-Oxide.—Phenanthridine (18·1 g.), dissolved in a little chloroform, was added to ethereal perphthalic acid solution (≈ 2·1 g. of active oxygen). After five days at 5° the solids were collected, ground with aqueous 5% ammonium hydroxide, and crystallised from ethanol (87%). *Phenanthridine 10-oxide* formed (after drying at 100°/20 mm.) leaflets, m. p. 220° (softening at 215°) (Found: C, 79·5; H, 4·6. $C_{13}H_9ON$ requires C, 80·0; H, 4·7%).

9-Methylphenanthridine 10-oxide hydrochloride was obtained (89%) in small buff prisms, m. p. 190—192° (decomp.; after drying) (Found: C, 68·1; H, 4·8. $C_{14}H_{12}ONCl$ requires C, 68·4; H, 4·9%).

9-Ethylphenanthridine 10-oxide monohydrate separated from aqueous acetic acid in pale pink needles, m. p. 252—253° (decomp.) (Found: C, 73·9; H, 6·3. $C_{15}H_{15}ON,H_2O$ requires C, 74·6; H, 6·3%).

9-Phenylphenanthridine 10-Oxide.—To a peracetic acid solution, prepared by heating 30% hydrogen peroxide (30 g.) and glacial acetic acid (50 g.) at 85° for one hour, was added 9-phenylphenanthridine (5·0 g.), and heating at 85° continued for a further 4—5 hours. The mixture was then poured into water, and the precipitated solids were collected and crystallised from chloroform. *9-Phenylphenanthridine 10-oxide* was obtained (91%) in glistening buff leaflets, m. p. 212—215° (Found: C, 84·4; H, 5·0. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%).

The compounds listed in Table IV were thus prepared.

9-p-Aminophenylphenanthridine 10-Oxide.—Finely powdered 9-*p*-nitrophenylphenanthridine 10-oxide (4·9 g.) was stirred with hydrochloric acid (25 ml.) on a steam-bath, a few drops of ethanol being added to prevent frothing. Stannous chloride (14 g.) in hydrochloric acid (15 ml.) was then added; the suspended solids dissolved and were replaced, after 30 minutes' heating, by yellow crystals. After cooling to 5° the separated stannichloride was collected and decomposed with 10% aqueous sodium hydroxide, and the liberated base crystallised from ethanol. *9-p-Aminophenylphenanthridine 10-oxide monohydrate* separated (40%) in yellow needles, m. p. 264—265° (decomp.) (Found: C, 75·2; H, 5·3. $C_{19}H_{14}ON_2,H_2O$ requires C, 75·0; H, 5·3%). The product is readily soluble in dilute acid and gives a positive primary amine test on diazotisation and coupling with alkaline 2-naphthol. For analysis the compound was dried at room temperature, as appreciable decomposition occurs at 100°.

9-m-Aminophenylphenanthridine 10-oxide hemihydrate formed yellow needles, m. p. 124—125° (decomp.) (Found: C, 77·8; H, 5·1; N, 9·0. $C_{19}H_{14}ON_2,\frac{1}{2}H_2O$ requires C, 77·3; H, 5·1; N, 9·5%), from ethanol.

3-Amino-9-methylphenanthridine 10-oxide hemihydrate was obtained (42%) in wispy yellow needles, m. p. 214° (Found: C, 72·3; H, 5·6. $C_{14}H_{12}ON_2,H_2O$ requires C, 72·1; H, 5·6%), from aqueous alcohol.

3-Amino-9-phenylphenanthridine 10-oxide monohydrate formed yellow needles (54%), m. p. 248° (decomp.) (Found: C, 75·5; H, 5·4. $C_{19}H_{14}ON_2,H_2O$ requires C, 75·0; H, 5·3%), from ethanol.

7-Amino-9-phenylphenanthridine 10-oxide separated (46%) in yellow needles, m. p. 278° (decomp.) (Found: C, 78·8; H, 5·3. $C_{19}H_{14}ON_2,\frac{1}{2}H_2O$ requires C, 78·0; H, 5·0%), from ethanol.

3-Diacetylamino-9-p-diacetylaminophenylphenanthridine 10-oxide hemihydrate, obtained in very low yield, separated from alcohol as an amorphous yellow powder, m. p. 258° (decomp., preheated bath) (Found: C, 67·7; H, 4·8. $C_{31}H_{26}O_5N_4,\frac{1}{2}H_2O$ requires C, 67·8; H, 5·1%).

9-4′-Pyridylphenanthridine 1′-Oxide.—The corresponding base was treated with 1·1 equivs. of perphthalic acid solution. After fractional crystallisation to remove unchanged material, the *1′-oxide* was obtained in prismatic needles, m. p. 266° (Found: C, 79·4; H, 4·6; N, 10·0. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4; N, 10·3%), from aqueous ethanol.

9-4′-Pyridylphenanthridine 10:1′-dioxide, colourless prisms (71%), m. p. 303° (decomp.) (Found: C, 75·3; H, 4·2. $C_{18}H_{12}O_2N_2$ requires C, 75·0; H, 4·2%), from ethoxyethyl alcohol, was similarly obtained by using 3·3 equivs. of perphthalic acid.

Quaternary Salts.—The base was heated with methyl sulphate for 10 minutes in nitrobenzene at 160°. The methosulphate was isolated either by direct filtration or by removal of the nitrobenzene by steam-distillation followed by concentration under reduced pressure. The compounds listed in Table V were thus prepared.

3-Amino-9-(2-phenyl-4-quinolyl)phenanthridine Dimethiodide.—3-Nitro-9-(2-phenyl-4-quinolyl)phenanthridine dimethosulphate (1·0 g.), dissolved in concentrated hydrochloric acid (5 ml.), was treated with stannous chloride (3 g.) in hydrochloric acid (4 ml.) for 2 hours on the water-bath. After cooling, the orange-red stannichloride was collected and decomposed with hydrogen sulphide in dilute hydrochloric acid solution. The resulting dimethochloride proved very hygroscopic. The *dimethiodide* was therefore prepared, and formed orange-red needles (0·9 g.), m. p. 228° (decomp.) (Found: C, 51·5; H, 4·2. $C_{30}H_{31}N_4I_2,H_2O$ requires C, 51·5; H, 3·9%), from aqueous ethanol.

2:3-Di-2′-furylquinoxaline.—Furil (9·5 g.), in hot ethanol (100 ml.) and chloroform (70 ml.), was heated with *o*-phenylenediamine (5·4 g.) in ethanol (10 ml.) under reflux for 30 minutes. Concentration gave *2:3-di-2′-furylquinoxaline*, yellow needles (12·6 g.), m. p. 130—131° (Found: C, 73·0; H, 3·4. $C_{18}H_{10}O_2N_2$ requires C, 73·3; H, 3·8%). Attempts to convert this compound into the *N*-oxide gave only 2:3-dihydroxyquinoxaline, white needles, m. p. >300° (Found: C, 59·0; H, 3·7. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7%), from water. Attempts to prepare quaternary salt were likewise unsuccessful.

2:3-Dimethylquinoline-4-carboxylic acid 1-oxide, prepared by using peracetic acid, formed glistening leaflets (25%), m. p. 229° (decomp.) (Found: C, 66·2; H, 5·1. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%), from ethanol.

2-Phenylquinoline-4-carboxylic acid 1-oxide, prepared similarly, formed pale yellow prisms (75%), m. p. 260° (decomp.) (Found: C, 71·7; H, 4·3. $C_{16}H_{11}O_3N$ requires C, 72·4; H, 4·2%).

2-Methyl-5:6-benzquinoline 1-oxide, prepared by treating 2-methyl-5:6-benzquinoline (10 g.) in glacial acetic acid (200 ml.) with hydrogen peroxide (50 ml. of 30%) at 50° for 24 hours, was obtained as the monohydrate, m. p. 87—89°, from which the oxide was obtained after drying, m. p. 128—129° (Found: C, 80·0; H, 5·8; N, 6·7. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·3; N, 6·7%).

The Action of Phosphorus Oxychloride on Some Phenanthridine N-Oxides.—*Phenanthridine 10-oxide.* The oxide (1·0 g.), in a flask cooled in ice–water was treated with phosphorus oxychloride (4·0 ml.) added dropwise with shaking. The mixture was then heated on the water-bath for 15 minutes, poured on

TABLE IV.

Phenanthridine 10-oxides.

Substituent.	M. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.	Description.*
9-p-*Tolyl-*	196—197°	50	$C_{20}H_{15}ON$	83·3	5·4	84·2	5·3	Buff needles [a]
9-o-*Chlorophenyl-*	209	91	$C_{19}H_{12}ONCl$	74·2	4·0	74·6	4·0	Buff leaflets [b]
9-p-*Chlorophenyl-*	252 (decomp.)	68	"	74·1	4·0	74·6	4·0	Cream leaflets [c]
3-*Chloro*-9-*phenyl-*	174—175	74	"	73·8	4·0	74·6	4·0	Pale yellow needles [d]
7-*Chloro*-9-*phenyl-*	218	66	"	74·5	4·2	74·6	4·0	Pale yellow prisms [d]
9-m-*Nitrophenyl-*	181	63	$C_{19}H_{12}O_2N_2$	71·5	3·8	72·1	3·8	Small buff needles [d]
9-p-*Nitrophenyl-*	242—245 (decomp.)	87	" ,H_2O	68·5	4·1	68·3	4·2	Golden needles [a]
3-*Nitro*-9-*phenyl-*	231	47	" ,H_2O	69·0	4·2	68·3	4·2	Yellow needles [a]
7-*Nitro*-9-*phenyl-*	269—271 (decomp.)	68	"	72·1	4·0	72·1	3·8	Yellow needles [a]
3-*Nitro*-9-m-*nitrophenyl-*	286	26	$C_{19}H_{11}O_3N_3$	63·4	3·3	63·2	3·1	Yellow needles [a] †
3-*Nitro*-9-*methyl-*	>265	96	(Could not be purified owing to insolubility. Used direct.)					
9-p-*Methoxyphenyl-*	232—234 (decomp.)	50	$C_{20}H_{15}O_2N$	78·9	4·7	79·7	5·0	Cream needles [d]

* Recrystallised from: [a] ethyl acetate, [b] aq. ethanol, [c] aq. acetic acid [d] ethanol, [e] acetic acid. † Period of heating, 16 hours.

TABLE V.

Phenanthridine quaternary salts.

Substituent.*	M. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.	Description.†
9-p-*Tolyl- M.S.*	191—192°	76	$C_{22}H_{21}O_4NS$	67·3	5·6	66·8	5·4	Needles [a]
9-p-*Tolyl- M.I.*	219—221 (decomp.)	76	$C_{21}H_{18}NI$	61·5	4·4	61·3	4·4	Yellow prisms [a]
9-o-*Chlorophenyl- M.I.*	207—208	60	$C_{20}H_{15}NClI$	55·9	3·7	55·7	3·5	Yellow prisms or red needles [b]
9-p-*Chlorophenyl- M.S.*	191—192	47	$C_{21}H_{18}O_4NSCl$	60·4	4·4	60·6	4·4	Needles [b]
9-[5-*Nitro*-2-*furyl*]- *M.S.*	210 (decomp.)	65	$C_{19}H_{14}O_7N_2S$	54·5	3·5	54·8	3·9	Yellow needles [b]
9-*Morpholinomethyl- M.S.*	206—207 (decomp.)	69	$C_{20}H_{24}O_5N_2S$	59·5	5·8	59·4	6·0	Needles [a]
9-*Morpholinomethyl- M.I.*	195 (decomp.)	69	$C_{18}H_{21}ON_2I$	54·8	5·5	54·3	5·0	Needles [a]
9-4′-*Pyridyl- M.S.*	171—174 (decomp.)	80	$C_{20}H_{15}O_4N_2S$	63·1	5·1	62·8	4·7	Cream leaflets [a]
9-4′-*Pyridyl- M.I.*	>290	57	$C_{18}H_{15}N_2I$	57·2	4·0	57·3	3·8	Yellow needles [c]
9-[2-*Phenyl*-4-*quinolyl*]- *di-M.S.*	230 (decomp.)	60	$C_{32}H_{26}O_8N_2S_2.2H_2O$	57·6	5·4	57·3	5·1	Yellow needles [a]
3-*Nitro*-9-[2-*phenyl*-4-*quinolyl*]- *di-M.S.*	260 (decomp.)	77	$C_{32}H_{28}O_{12}N_4S_2.2H_2O$	53·7	4·7	54·2	4·9	Yellow prisms [b]
7-*Nitro*-9-[2-*phenyl*-4-*quinolyl*]- *di-M.S.*	254—255 (decomp.)	70	$C_{32}H_{28}O_{12}N_4S_2$	56·3	4·4	56·5	4·3	Small yellow needles [b]

* M.I. = methiodide; M.S. = methosulphate. † Recrystallised from: [a] ethanol–ether, [b] ethanol, [c] aqueous ethanol.

ice, and neutralised with sodium hydroxide. The product in light petroleum (50 ml. of b. p. 80—100°; charcoal) deposited a little phenanthridone on storage overnight; this was removed, and the filtrate chilled to −30°. 9-Chlorophenanthridine separated, needles (0·95 g.), m. p. 116·5° (Found: C, 73·1; H, 3·8. Calc. for $C_{13}H_8NCl$: C, 73·1; H, 3·8%), from light petroleum, not depressed in admixture with an authentic specimen.

9-Chlorophenanthridine (10 g.) in alcohol (50 ml.) was added to a solution of sodium (1·2 g.) in alcohol (50 ml.), and the mixture heated under reflux for 3 hours. The product, in light petroleum, was purified by passage through a column of alumina, giving 9-*ethoxyphenanthridine*, needles (2·5 g.), m. p. 60° (Found: C, 80·5; H, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9), from methanol. On reaction with peracetic acid it was converted into phenanthridone.

9-*Phenylphenanthridine* 10-*oxide*. The oxide (2·0 g.) in a flask cooled in ice-water, was treated dropwise with phosphorus oxychloride (8 ml.). When the vigorous reaction had subsided the mixture was heated on the water-bath for 1½ hours, and the product isolated as before. Repeated crystallisation from methanol gave 3-chloro-9-phenylphenanthridine, m. p. 141° (Found: C, 79·0; H, 4·2. Calc. for $C_{19}H_{12}NCl$: C, 78·7; H, 4·3%), not depressed in admixture with an authentic specimen.

9-*Methylphenanthridine* 10-*oxide*. The oxide hydrochloride (2·0 g.) was treated with phosphorus oxychloride (8 ml.) as before, and the mixture heated on the water-bath for 45 minutes. After decomposition with ice and basification with ammonia, the product was fractionated from ethanol, giving 9-chloromethylphenanthridine, m. p. 132° (Found: C, 74·2; H, 4·6. Calc. for $C_{14}H_{10}NCl$: C, 73·8; H, 4·4%), not depressed in admixture with an authentic specimen. The mother-liquors yielded (? 3-)*chloro*-9-*methylphenanthridine*, small needles, m. p. 91·5—92·5° (Found: C, 73·3; H, 4·6%), from light petroleum.

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CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, December 5th*, 1949.]

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143. 9 : 10-*Dihydrophenanthrenes. Part I. The Formation of* 9 : 10-*Dihydrophenanthrene from* 2 : 2′-*Disubstituted Diphenyls.*

By D. MURIEL HALL, MARY S. LESSLIE, and E. E. TURNER.

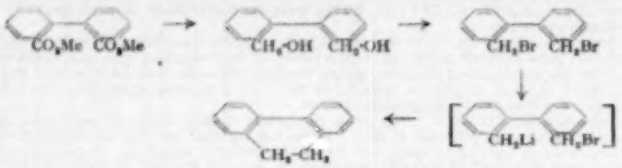
9 : 10-Dihydrophenanthrene is formed in high yield by the action of phenyl-lithium on 2 : 2′-di(bromomethyl)diphenyl, which is smoothly formed from the corresponding dihydroxy-compound. The latter is formed in almost quantitative yield by reducing alkyl diphenates with ethereal lithium aluminium hydride. Dihydrophenanthrene is formed in considerable quantities when the di(bromomethyl)diphenyl reacts with magnesium in the presence of ether.

THE most obvious routes to 9 : 10-dihydrophenanthrene are (*a*) the catalytic hydrogenation of phenanthrene and (*b*) the Wurtz–Fittig process from 2 : 2′-di(halogenomethyl)diphenyls. Burger and Mosettig (*J. Amer. Chem. Soc.*, 1935, **57**, 2731; 1936, **58**, 1857) obtained the hydrocarbon by the catalytic hydrogenation of phenanthrene, but the experimental conditions are beyond present resources. Dihydrophenanthrene must have been present in considerable quantities in the liquid product obtained by Kenner and Turner (*J.*, 1911, **99**, 2101) by the action of sodium on 2 : 2′-di(bromomethyl)diphenyl, since oxidation of the crude product gave a 26% yield of phenanthraquinone. Kenner and Turner were misled in their conclusions by the inaccurate work of Schmidt and Mezger (*Ber.*, 1907, **40**, 4240) who described 9 : 10-dihydrophenanthrene as a solid melting at 94—95°. Schroeter, Müller, and Huang (*Ber.*, 1929, **62**, 645) obtained 3 g. of dihydrophenanthrene, m. p. 34·5—35°, by the action of sodium on 25 g. of 2 : 2′-di(bromomethyl)diphenyl.

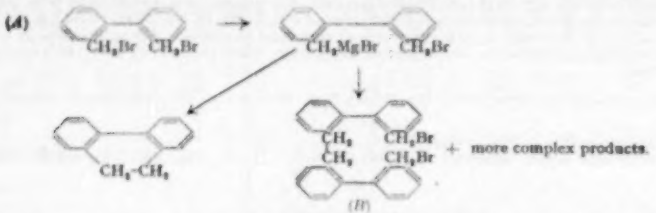
It is now found that although Kenner's conditions for the side-chain bromination of 2 : 2′-ditolyl cannot be materially improved, 2 : 2′-ditolyl can be obtained in 65% yield by heating *o*-iodotoluene with activated copper powder (Kleiderer and Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 4219), a suitable alternative route being the Krizewsky–Turner reaction (*J.*, 1919, **115**, 559; *J. Proc. Roy. Soc. N.S.W.*, 1920, **54**, 37) with *o*-bromotoluene, when a yield of not less than 35% of ditolyl is obtained. Curiously enough, cupric chloride reacts indifferently with *o*-tolylmagnesium iodide, the main product of an attempted Krizewsky–Turner reaction with the latter being toluene, representing non-reaction.

As already indicated (*Nature*, 1949, **163**, 537), a more practicable route to 9 : 10-dihydrophenanthrene is the reduction of methyl diphenate by means of lithium aluminium hydride to 2 : 2′-di(hydroxymethyl)diphenyl, followed by conversion of the latter into 2 : 2′-di(bromo-

methyl)diphenyl and the interaction of this bromo-compound with phenyl-lithium. In this way, a 70% yield of dihydrophenanthrene from methyl diphenate is readily obtained.



When an attempt is made to prepare a Grignard reagent from 2 : 2′-di(bromomethyl)diphenyl (*A*) a mixture is obtained, the annexed scheme suggesting a probable sequence of reactions :



In the presence of either 2·2 or 1·0 atomic proportions of magnesium, 40% of the product is dihydrophenanthrene, the remainder containing high-melting products of which the main component appears to be 1 : 2-di-(2′-bromomethyl-2-diphenylyl)ethane (*B*), hydrolysable to 1 : 2-*di*-(2′-*hydroxymethyl*-2-*diphenylyl*)*ethane*.

Experimental.

2 : 2′-*Ditolyl*.—(*a*) Activated copper bronze was heated in a bath kept at about 260° and *o*-iodotoluene (50 g.) added at infrequent intervals. Heating was continued until refluxing ceased (about 20 hours). The somewhat cooled mixture was extracted with boiling chlorobenzene, and the filtered extract distilled. No unchanged iodotoluene was found. The main portion boiled at 254—256° and was almost pure ditolyl (13·5 g., 65% yield). Some commercial samples of copper bronze were found to be without perceptible action on boiling iodotoluene, even after attempted activation.

(*b*) A solution of *o*-tolylmagnesium bromide was prepared from 171 g. (1 g.-mol.) of *o*-bromotoluene and 24·5 g. of magnesium, in *ca.* 800 c.c. of ether. Finely-ground anhydrous cupric chloride (170 g.; 1·25 g.-mols.) was gradually added and the resulting mixture boiled for an hour. Ice and then concentrated hydrochloric acid were added and later (to oxidise the cuprous salts and render subsequent operations easier) about one g.-mol. of ferric chloride (about 400 g. of the dodecahydrate) in concentrated aqueous solution. The two layers were separated and the aqueous layer extracted several times with ether. The combined ethereal extracts were washed with water and alkali and fractionally distilled in steam. Fractions were cooled to about 10°. Oils which solidified were filtered and were pure ditolyl, m. p. 18°. Other fractions were separated or extracted with ether, and the dried ether extracts distilled. High-boiling materials (above 190°) were steam-distilled and the fractions treated as before. From a series of such operations, 836 g. of bromotoluene gave 156 g. (35% yield) of ditolyl, m. p. 18°, the highest individual yield being 42%.

Bromination of 2 : 2′-*Ditolyl*.—Ditolyl (9 g., 1 g.-mol.) was heated at 125—130° in a current of dry nitrogen which had bubbled slowly through 5·5 c.c. of bromine (just over 2 g.-mols.). Bromination took several hours, after which the product was cooled, stirred with dry light petroleum (b. p. 60—80°), and crystallised from this solvent. The process was not noticeably accelerated or improved if a trace of benzoyl peroxide was present. In all, 153·5 g. of ditolyl were brominated and gave 125·5 g. of 2 : 2′-di(bromomethyl)diphenyl, m. p. 89—92° (yield, 44%). One further crystallisation from light petroleum gave 119 g. of pure dibromide, m. p. 91—93°.

2 : 2′-*Di*(*hydroxymethyl*)*diphenyl*.—A solution of 76 g. of methyl diphenate in 700 c.c. of dry ether was added as fast as refluxing permitted to a solution of 17 g. of lithium aluminium hydride (1·6 g.-mols.) in 600 c.c. of ether. Water and then dilute sulphuric acid were added and the mixture freed from ether by heating on a water-bath. After the mixture had cooled, the solid was filtered off, washed, and dried. The *hydroxymethyl* compound crystallised from benzene in needles, m. p. 112—113° (yield, 55 g., 91%) (Found : C, 77·9; H, 6·8. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

Similar reduction of ethyl diphenate gave a 93% yield of diol.

2 : 2′-*Di*(*bromomethyl*)*diphenyl*.—The dihydroxyditolyl (15 g.) was added gradually to 750 c.c. of 46% hydrobromic acid at 90° and the mixture then boiled for 20 minutes. On cooling, a crystalline meal was formed and this was filtered off. The solid was dried *in vacuo* and crystallised from light

petroleum (b. p. 60—80°). From three such operations 67 g. (94% yield) of pure dibromo-compound were obtained.

9 : 10-*Dihydrophenanthrene*.—Freshly made lithium wire (3 g.) were cut into a nitrogen-filled flask containing 150 c.c. of dry ether, and 32 g. of bromobenzene were then gradually added. When interaction was complete, a solution of 54 g. of dibromoditolyl in 450 c.c. of ether was added as fast as refluxing allowed. Ice and water were then introduced and the two layers separated. Distillation of the dried ethereal solution gave 24·5 g. (86% yield) of dihydrophenanthrene, b. p. 174°/17 mm. After one crystallisation from methyl alcohol the hydrocarbon had m. p. 35·0—35·5°.

Action of Magnesium on 2 : 2′-Di(bromomethyl)diphenyl.—(*a*) The dibromo-compound (17 g.) reacted in ethereal solution with 0·5 atomic proportion of magnesium which had previously been activated with ethyl bromide. A further 0·5 atomic proportion of magnesium was added and the mixture boiled for 2 hours. A violet colour appeared at one stage and later disappeared. A white solid separated. Water and dilute hydrochloric acid were added without cooling and the solid separated and dried (4·4 g.). Crystallisation from a mixture of *cyclo*hexanone and light petroleum (b. p. 100—120°) gave 1 : 2-*di*-(2′-*hydroxymethyl*-2-*diphenylyl*)*ethane*, micro-crystalline, m. p. 242—244°, darkening at 235° [Found: C, 84·7; H, 6·8%; *M* (cryoscopic, in camphor), 422. $C_{28}H_{26}O_2$ requires C, 85·25; H, 6·65%; *M*, 394·5]. The ethereal layer, after being dried and distilled, gave 3·5 g. of dihydrophenanthrene (40%).

(*b*) Dibromoditolyl (34 g.) reacted in ethereal solution with 0·5 atomic proportion of activated magnesium and after further addition of 0·5 atomic proportion of magnesium the mixture was boiled for 6 hours. The white solid which separated was filtered off, washed with 47% hydrobromic acid, and dried (5·4 g.). The mixture of bromo-compounds obtained could not be separated, but crystallisation from a moist mixture of *cyclo*hexanone and light petroleum (b. p. 100—120°) gave the diol (m. p. 242—244°). From the ethereal mother-liquor 7·2 g. of dihydrophenanthrene were obtained.

(*c*) An ethereal solution of 17 g. of dibromoditolyl was boiled for several hours with 2·64 g. (2·2 atomic proportions) of activated magnesium. As in (*a*) and (*b*) a violet colour appeared intermediately and a solid separated. The yield of dihydrophenanthrene was 40%.

Our thanks are due to Imperial Chemical Industries Ltd. for a grant and to Dr. V. A. Petrow, of the British Drug Houses Ltd., for a gift of diphenic esters.

UNIVERSITY OF LONDON (BEDFORD COLLEGE). [*Received, December 6th*, 1949.]

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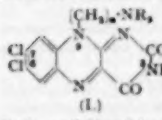
144. *A Series of 9-Dialkylaminoalkylisoalloxazines.*

By R. B. BARLOW and H. R. ING.

A series of 6 : 7-dichloro-9-dialkylaminoalkyl*iso*alloxazines and some related compounds have been prepared and tested as antimalarial and trypanocidal agents.

SINCE 1945 numerous papers have appeared describing the preparation of *iso*alloxazine derivatives containing a basic side chain (Hall and Turner, *J.*, 1945, 699; Neeman, *J.*, 1946, 811; King and Acheson, *J.*, 1946, 681; 1948, 1926; Adams, Weisel, and Mosher, *J. Amer Chem. Soc.*, 1946, **68**, 883; Kipnis, Weiner, and Spoerri, *ibid.*, 1947, **69**, 799; Burkett, *ibid.*, 1947, **69**, 2555; Hippchen, *Ber.*, 1947, **80**, 263). When the work to be described herein was begun, in May 1944, it was proposed to prepare 6 : 7-dichloro*iso*alloxazines (I) with a basic side chain attached in the 9-position in the hope that they would prove to have antimalarial activity. It was known that mepacrine antagonized riboflavin in some micro-organisms and the 6 : 7-dichloro-compounds were chosen for the same reason as led Kuhn, Weygand, and Möller (*Ber.*, 1943, **76**, 1044) to synthesise the 6 : 7-dichloro-analogue of riboflavin, although at the time this work of the German authors was unknown to us.



(I.)

The first compound to be prepared, 9-(3′-*piperidinopropyl*)-6 : 7-*dichloroisoalloxazine hydrochlorides* (I; $n = 3$, $NR_2 = N{<}C_5H_{10}$), gave promise of being a member of an interesting new series; it was tested (serial number 5115) in the laboratories of Imperial Chemical Industries Ltd., and found by Dr. D. G. Davey to have definite antimalarial activity against *Plasmodium gallinaceum* in chicks, and by Dr. J. Madinaveitia to exert an antibacterial action against *Lactobacillus casei*, which was to some extent antagonized by riboflavin. Later, Dr. Davey found that the same substance had some trypanocidal activity *in vitro*, but not *in vivo* (against *Trypanosoma rhodesiense*).

After some delay the work was resumed and Table I gives a list of the *compounds* prepared. The first four differ only in the length of the polymethylene chain. One 7-chloro-compound (8021) and one 6-chloro-compound (5374) were prepared for comparison with their dichloro-analogues, 5115 and 5291, respectively. The 6 : 7-dichloro-3-methyl compound (8956) was made in order to discover the effect of blocking the possibility of lactam–lactim tautomerism in the *iso*alloxazine nucleus, and the methochloride (8955) to discover the effect of quaternizing the basic group; compound 8957 combines both these structural changes. Some difficulty was

encountered in preparing the last compound in Table I, which contains the same side chain as mepacrine, and it has so far only been tested *in vitro*.

TABLE I.

iso*Alloxazines*.

Serial number.	Substituents in positions: 5.	6.	7.	9.	pK_a (±0·3) at 21°.
8776	—	Cl	Cl	$[CH_3]_2$·$NHEt_2$]Cl	7·7
5291	—	Cl	Cl	$[CH_3]_2$·$NHEt_2$]Cl	9·1
8778	—	Cl	Cl	$[CH_3]_2$·$NHEt_2$]Cl	9·7
8779	—	Cl	Cl	$[CH_3]_2$·$NHEt_2$]Cl	9·6
5115	—	Cl	Cl	$[CH_3]_2$·NH<C_5H_{10}]Cl	8·9
8021	—	—	Cl	$[CH_3]_2$·NH<C_5H_{10}]Cl	9·0
5374	—	Cl	—	$[CH_3]_2$·$NHEt_2$]Cl	9·8
8777	—	Cl	Cl	$[CH_3]_2$·$NHBu_2$]Cl	8·0
8955	—	Cl	Cl	$[CH_3]_2$·$NMeEt_2$]Cl	—
8956	Me	Cl	Cl	$[CH_3]_2$·$NHEt_2$]Cl	9·7
8957	Me	Cl	Cl	$[CH_3]_2$·$NMeEt_2$]Cl	—
9163	—	Cl	Cl	CHMe·$[CH_3]_2$·$NHEt_2$]X •	9·6

• X = Picrate anion.

The compounds were tested as antimalarial and trypanocidal agents in the laboratories of Imperial Chemical (Pharmaceuticals) Ltd. through the courtesy of the late Dr. F. H. S. Curd and Dr. D. G. Davey, but none of the compounds fulfilled the expectations aroused by the early tests on 5115; nor in later tests did the latter substance prove to be so active an antimalarial as had at first been thought. The 7-chloro-compound (8021) had slight activity against *T. congolense* in mice, and so had the quaternary salt 8955. The two 3-methyl compounds had slight to moderate activity against *T. rhodesiense* in mice, but none of the other compounds had any curative action against either parasite *in vivo*. The lack of curative activity in experimental malaria and trypanosomiasis may be partly due to the high toxicity of these compounds to chicks and mice, since positive effects were only observed with doses within the toxic range. The cause of this toxicity is unknown, but an action on the central nervous system is suspected.

The compounds were also tested in this laboratory, with the help of Dr. E. M. Lourie, against *T. rhodesiense in vitro*; they were trypanocidal in a dilution range of 1—2·5 million. Dr. Lourie tells us that with the same organism stilbamidine and pentamidine are trypanocidal in the ranges 1—4 and 6—8 million respectively (unpublished results), whereas undecanediamidine and tervalent arsenicals are active in dilutions of 1 in 100 million or more (King, Lourie, and Yorke, *Ann. Trop. Med. Parasit.*, 1938, **32**, 177).

On three flavoprotein enzymes, *viz.*, D-amino-acid oxidase, monoamine oxidase, and diamine oxidase, these compounds exerted only feeble inhibition; they had, however, the peculiar property of increasing the oxygen uptake of certain enzyme preparations, in particular those prepared from acetone-dried powders of liver and kidney. Dr. Madinaveitia had previously observed that, whereas 5115 inhibited the alcohol, citrate, and glycerophosphate dehydrogenases of yeast, yet it accelerated the action of yeast lactic acid dehydrogenase.

The pK_a values of all the tertiary bases were measured by the method of Albert and Goldacre (*J.*, 1943, 454); the results, included in Table I, are subject to an error of ±0·3 owing to the use of a mains-operated meter.

Professor Adrien Albert very kindly tested two of our compounds (5291 and its 3-methyl derivative 8956) for chelation effects by electrometric titration in the presence of cupric chloride. He reports that neither of these gave evidence of chelation; both behaved in the same way, although the former contains the unit ·N:C·C(OH):N·, which might be expected to give rise to chelation, and the latter does not.

With the exception of the substance containing the 4-diethylamino-1-methylbutyl side chain, all the isoalloxazines were prepared by condensing suitably substituted *o*-phenylenediamines with alloxan monohydrate in methanol containing hydrogen chloride (Kuhling, *Ber.*, 1891, **24**, 2363); they were isolated as their crystalline *hydrochlorides*, which were usually hydrated, and occasionally as their *picrates*. The *o*-phenylenediamine derivatives were not usually isolated; they were obtained by catalytic reduction of the corresponding *o*-nitroaniline derivative in methanol and, after the removal of the catalyst, they were immediately condensed with alloxan. At first the *o*-nitroaniline derivatives were prepared by heating the appropriate ω-dialkylaminoalkylamine with 4 : 5-dichloro-1 : 2-dinitrobenzene, but as the preparation of the latter substance in quantity

is exceedingly tedious (cf. Kuhn, Weygand, and Möller, *loc. cit.*), it was replaced by 2 : 4 : 5-trichloronitrobenzene, which is readily obtained by nitrating 1 : 3 : 4-trichlorobenzene; that it is the chloro-substituent *ortho* to the nitro-group which is replaced by the substituted alkylamine was proved by preparing three of the nitroaniline derivatives from both of these starting materials (see Table II). The *o*-nitroaniline derivatives were usually isolated as hydrochlorides or perchlorates, but reduction (with hydrogen and Raney nickel at atmospheric pressure) was best effected with the free bases in methanol; reduction of the hydrochlorides with hydrogen and palladium–charcoal was exceedingly slow.

The 6-chloro-compound (5374) was prepared by condensing 5-chloro-2-iodonitrobenzene with diethylaminopropylamine, reducing the *o*-nitroaniline derivative so formed, and condensing the product with alloxan. The 7-chloro-compound (8021) was similarly prepared from 2 : 4-dichloronitrobenzene and piperidinopropylamine.

Quaternary metho-salts of 9-dialkylaminoalkylisoalloxazines could not be obtained by direct addition of methyl iodide to the free bases, or by condensing alloxan with the reduction products of *o*-nitro-*N*-dialkylaminoalkylaniline methiodides; intractable red products were formed by both methods. When, however, the *o*-nitro-*N*-dialkylaminoalkylaniline was converted into its methochloride (by the addition of methyl sulphite and subsequent hydrolysis of the metho-methylsulphite with hydrochloric acid), condensation with alloxan was satisfactorily effected after reduction of the nitro-group. The 3-methylisoalloxazines were prepared by using methylalloxan in place of alloxan.

6 : 7-Dichloro-9-(4-diethylamino-1-methylbutyl)isoalloxazine hydrochloride could not be obtained by condensing the appropriate *o*-phenylenediamine derivative with alloxan in methanol containing hydrogen chloride; the only product isolated was 6 : 7-*dichloroalloxazine*. Other authors have found a similar difficulty in preparing isoalloxazines with the "mepacrine side chain" in position 9 (cf. Hall and Turner, *loc. cit.*; Kipnis, Weiner, and Spoerri, *loc. cit.*; McCombrey and Webster, *J.*, 1948, 1719), and Neeman (*loc. cit.*), who used boric acid in acetic acid as the condensing agent (Kuhn and Weygand, *Ber.*, 1935, **68**, 1282), was only able to isolate his products as reineckates. Condensation of alloxan with the reduction product of 4 : 5-*dichloro*-2-(4-*diethylamino*-1-*methylbutylamino*)*nitrobenzene* certainly occurs in acetic acid solution in the presence of boric acid, since we were able to isolate the isoalloxazine as its *picrate*, but we were unable to isolate the hydrochloride in an analytically pure state.

Experimental.

(All analyses are by Drs. Weiler and Strauss. All m. p.s are uncorrected.)

Dialkylaminoalkylamines.—We are indebted to Messrs. Imperial Chemical Industries Ltd. for generous supplies of diethylamino-ethylamine and -propylamine, dibutylaminopropylamine, and 4-diethylamino-1-methylbutylamine. Diethylamino- and piperidino-propylamines were prepared by the method of Whitmore *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 725), the intermediate nitriles being reduced by sodium and ethanol. Diethylaminobutylamine was prepared from γ-chlorobutyronitrile (Utermohlen and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 156; Strukov, *Chem. Abs.*, 1934, **28**, 3714), and the homologous amylamine from phthalo-5-bromoamylimide (Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396).

2-*Nitro*-N-*dialkylaminoalkylanilines.*—The 4 : 5-dichloro-2-nitrodialkylaminoalkylanilines were all prepared by boiling a solution of the dialkylaminoalkylamine and 2 : 4 : 5-trichloronitrobenzene (10% excess) in toluene or xylene for 5—12 hours; yields of 40—50% were obtained. Three of them (see Table II) were also prepared in a similar way from the alkylamine and 4 : 5-dichloro-1 : 2-dinitrobenzene. 5-*Chloro*-2-*nitro*-N-3′-*piperidinopropylaniline hydrochloride* was obtained similarly from piperidinopropylamine and 2 : 4-dichloronitrobenzene. The reaction mixtures were cooled and shaken with dilute hydrochloric acid; if the solid hydrochloride separated, it was collected and crystallized from water or alcohol; otherwise, the free base was liberated to ether and converted into the perchlorate. Only one base was obtained crystalline, *viz.*, 4 : 5-*dichloro*-2-*nitro*-N-2′-*diethylaminoethylaniline*.

4-*Chloro*-2-*nitro*-N-3′-*diethylaminopropylaniline hydriodide* was obtained by heating together diethylaminopropylamine and 5-chloro-2-iodonitrobenzene (Korner, *Gazzetta*, 1875, **4**, 381) without a solvent at 100° until a test drop gave a clear solution in dilute acid (4 hours). The product was diluted with water and acidified with hydriodic acid, the salt then crystallizing; it was recrystallized by the addition of ether to its solution in hot ethanol.

Table II gives a list of the compounds prepared, their m. p.s, and analytical results. The salts tend to crystallize in orange or yellow hydrated forms; the anhydrous salts are red, but become yellow in a damp atmosphere. The hydrochlorides are soluble in water and alcohol, but only sparingly so in acetone; the perchlorates are less soluble in water and alcohol. The *methochloride* of 4 : 5-dichloro-2-nitro-*N*-3′-diethylaminopropylaniline was obtained by heating the free base in methanol with methyl sulphite (1 mol.; excess must be avoided); after 1 hour, excess of hydrochloric acid was added, and heating continued for 4 hours; the solution was then evaporated and the residue taken up in ethanol and again evaporated; it was finally crystallized from ethanol. Both the methochloride (orange) and the *methiodide* (yellow) were hydrated; they lost water, becoming red, a few degrees above 100°.

2 : 4 : 5-Trichloronitrobenzene was prepared by adding 1 : 2 : 4-trichlorobenzene (25 c.c.) gradually to nitric acid (*d* 1·5; 120 c.c.) cooled in ice–salt; the solution was poured on ice, and the mixture left at 0°

TABLE II.

2-Nitro-N-dialkylaminoalkylanilines.

Method.	Substituents. 4.	5.	N.	Salt.	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
a	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	—	102° •	$C_{12}H_{17}O_2N_3Cl_2$	47·1	5·4	—	47·1	5·6	—
a, *b*	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	214	$C_{13}H_{20}O_2N_3Cl_3$ †	—	—	11·5	—	—	11·8
				MeI	215	$C_{14}H_{22}O_2N_3Cl_2I,H_2O$	35·0	5·0	—	35·0	5·0	—
				MeCl	216	$C_{15}H_{22}O_2N_3Cl_3,H_2O$	43·2	5·7	—	43·3	6·2	—
a	Cl	Cl	$[CH_2]_4{\cdot}NEt_2$	HCl	133 ‡	$C_{14}H_{22}O_2N_3Cl_3,\frac{1}{2}H_2O$	44·2	6·1	10·8	44·3	6·1	11·1
				$HClO_4$	143 ‡	$C_{14}H_{22}O_6N_4Cl_2$	—	—	9·8	—	—	9·7
a	Cl	Cl	$[CH_2]_5{\cdot}NEt_2$	$HClO_4$	123 ‡	$C_{15}H_{24}O_6N_4Cl_2$	39·7	4·9	—	40·2	5·4	—
a, *b*	Cl	Cl	$[CH_2]_3{\cdot}NC_5H_{10}$	HCl	215	$C_{14}H_{20}O_2N_3Cl_3$	—	—	11·2	—	—	11·4
a	Cl	Cl	$[CH_2]_3{\cdot}NBu_2$	$HClO_4$	140 ‡	$C_{17}H_{26}O_6N_4Cl_2$	42·9	5·8	—	42·8	5·9	—
a, *b*	Cl	Cl	$CHMe{\cdot}[CH_2]_2{\cdot}NEt_2$	$HClO_4$	109	$C_{15}H_{24}O_6N_4Cl_2$	—	—	9·5	—	—	9·4
c	Cl	H	$[CH_2]_3{\cdot}NEt_2$	HI	157	$C_{13}H_{21}O_2N_3ClI$	37·9	5·0	—	37·7	5·1	—
d	H	Cl	$[CH_2]_3{\cdot}NC_5H_{10}$	HCl §	210	$C_{14}H_{21}O_2N_3Cl_2$	49·3	6·0	—	49·0	6·4	—

(*a*) Prepared from 2 : 4 : 5-trichlorobenzene. (*b*) Prepared from 4 : 5-dichloro-1 : 2-dinitrobenzene.
(*c*) Prepared from 5-chloro-2-iodonitrobenzene. (*d*) Prepared from 2 : 4-dichloronitrobenzene.
• Free base, crystallized from ether. † Found : Cl, 29·8. $C_{13}H_{20}O_2N_3Cl_3$ requires Cl, 29·9%.
‡ Melting with decomposition.
§ Crystallized with $\frac{1}{2}H_2O$ (Found : H_2O, 2·7. $C_{14}H_{20}O_2N_3Cl,HCl,\frac{1}{2}H_2O$ requires H_2O, 2·6%) but the analysis in the Table is for the anhydrous salt.

TABLE III.

9-Dialkylaminoalkylisoalloxazines.

Substituents: 3.	6.	7.	9.	Salt.	Cryst. from	M. p.*	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
—	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	HCl	H_2O–MeOH	286°	$C_{19}H_{19}O_2N_5Cl_2,\frac{1}{2}H_2O$	46·0	4·4	16·6	45·9	4·1	16·7
CH_3	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	HCl	H_2O–EtOH	244	$C_{17}H_{20}O_2N_5Cl_2,H_2O$	45·8	4·9	15·6	45·3	4·9	15·6
—	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	H_2O–EtOH	244	$C_{17}H_{20}O_2N_5Cl_2,H_2O$	45·5	4·9	15·6	45·3	4·9	15·6
				HCl †	MeOH–Et_2O	244	$C_{17}H_{20}O_2N_5Cl_2,1\frac{1}{2}H_2O$	43·9	5·0	15·0	44·4	4·6	15·2
				MeCl	H_2O–EtOH	276	$C_{18}H_{22}O_2N_5Cl_3,2H_2O$	44·1	5·0	15·0	44·8	5·4	14·5
				Me p.‡	H_2O–EtOH	130	$C_{26}H_{24}O_6N_8Cl_2,H_2O$	43·8	3·7	17·1	43·8	3·9	17·0
CH_3	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	EtOH	240	$C_{19}H_{23}O_2N_5Cl_2,1\frac{1}{2}H_2O$	45·3	4·8	15·3	45·6	5·3	14·8
				p. ¶	H_2O–EtOH	215	$C_{26}H_{24}O_6N_8Cl_2$	44·6	3·1	17·7	45·1	3·8	17·8
				MeCl	H_2O–EtOH	248	$C_{19}H_{24}O_2N_5Cl_3,\frac{1}{2}H_2O$	48·2	5·0	15·3	48·6	5·3	14·9
				Me p.	EtOH	204	$C_{20}H_{26}O_6N_8Cl_2$	45·5	3·8	17·3	46·0	4·0	17·2
—	Cl	Cl	$[CH_2]_4{\cdot}NEt_2$	HCl	H_2O–EtOH	259	$C_{19}H_{23}O_2N_5Cl_2,1\frac{1}{2}H_2O$	45·8	5·1	15·1	45·7	5·3	14·8
				p.	H_2O–EtOH	236	$C_{26}H_{24}O_6N_8Cl_2$	45·3	4·0	17·1	45·1	3·8	17·5
—	Cl	Cl	$[CH_2]_5{\cdot}NEt_2$	HCl	AcOH	252	$C_{19}H_{23}O_2N_5Cl_2,H_2O$	47·5	5·0	13·9	47·7	5·4	14·6
				p.	H_2O–EtOH	247	$C_{25}H_{24}O_6N_8Cl_2$	46·3	4·0	17·3	46·0	4·0	17·2
—	Cl	Cl	$[CH_2]_3{\cdot}N{<}C_5H_{10}$	HCl §	AcOH–Et_2O	271	$C_{19}H_{23}O_2N_5Cl_2,H_2O$	46·9	5·0	15·1	46·7	4·8	15·1
—	Cl	Cl	$[CH_2]_3{\cdot}NBu_2$	HCl	EtOH	246	$C_{21}H_{27}O_2N_5Cl_2,\frac{1}{2}H_2O$	50·5	6·1	13·8	50·5	5·8	14·1
				p.	EtOH–$COMe_2$	223	$C_{27}H_{26}O_6N_8Cl_2$	47·5	4·8	16·4	47·6	4·4	16·4
—	Cl	Cl	$CHMe{\cdot}[CH_2]_2{\cdot}NEt_2$	p.	EtOH–$COMe_2$	209	$C_{25}H_{24}O_6N_8Cl_2$	45·6	4·6	17·2	46·0	4·0	17·2
—	Cl	—	$[CH_2]_3{\cdot}NEt_2$	HCl	AcOH–$COMe_2$	282	$C_{17}H_{21}O_2N_5Cl_2$	50·9	4·9	17·7	51·2	5·3	17·6
—	—	Cl	$[CH_2]_3{\cdot}N{<}C_5H_{10}$	HCl	AcOH	275	$C_{18}H_{21}O_2N_5Cl_2$	52·4	5·3	16·6	52·6	5·1	17·1

• All salts melt with decomposition. † Found : H_2O, 5·8. $C_{17}H_{20}O_2N_5Cl_2,1\frac{1}{2}H_2O$ requires H_2O, 5·9%.
‡ Found : H_2O, 2·3. $C_{26}H_{24}O_6N_8Cl_2,H_2O$ requires H_2O, 2·7%. § Found : H_2O, 3·9. $C_{19}H_{23}O_2N_5Cl_2,H_2O$ requires H_2O, 3·9%.
¶ p. = picrate.

overnight. The solid was collected, sucked as dry as possible from oily products, and crystallised twice from methanol; m. p. 57°; yield 20 g., 50—60% (Jungfleisch, *Ann. Chim. Phys.*, 1868, **15**, 273).

The iso-Alloxazine Condensation.—The 2-nitro-alkylaminoalkylanilines were liberated from their salts to ether, the ethereal extracts dried (Na_2SO_4) and evaporated, and the free bases dissolved in methanol and reduced with hydrogen and Raney nickel at atmospheric pressure. After removal of the catalyst, hydrogen chloride was bubbled into the solution, and alloxan monohydrate (1 mol.) added; the hydrogen chloride stream was continued until the blue colour, which formed round the alloxan crystals, had disappeared and the solution was strongly acid to Congo-red. Sufficient heat was usually generated by this procedure to effect dissolution of the alloxan, but occasionally additional heating was necessary. The deep-brown solution was set aside for at least 12 hours. The *iso*alloxazine hydrochloride sometimes crystallised from the reaction mixture; if not, it was precipitated as a dark brown oil or gum by addition of ether; the mother-liquor from any crystalline material was also treated in this way. The gummy salt often crystallized when stirred with ethanol, but sometimes further washing with ether or acetone was necessary before crystallization could be induced. The *hydrochlorides* were all readily soluble in water with a brilliant green fluorescence, but sparingly so in ethanol. They were usually crystallised from aqueous ethanol and, with the exception of the 6-chloro- and the 7-chloro-compound, they were all hydrated; the two *methochlorides* behaved similarly. The *picrates*, with one exception, crystallized anhydrous and provided a convenient way of characterising these *iso*alloxazine derivatives. Table III gives a list of the compounds prepared, with m. p.s and analytical results. Usually the yield of recrystallised product was about 30—40%.

4 : 7-Dichloro-9-(4-diethylamino-1-methylbutyl)*iso*alloxazine was prepared in a crude state from the appropriate *o*-nitroaniline derivative by the method of Kipnis, Weiner, and Spoerri (*loc. cit.*). Several attempts were made to prepare a hydrochloride from the crude base, but without success. The *picrate*, however, crystallized from aqueous alcohol–acetone (Table III). When methanolic hydrogen chloride was used as the condensing medium, an insoluble white product separated which appeared to be **6** : 7-*dichloroalloxazine*; it was insoluble in all the usual solvents, but dissolved in aqueous alkali and was reprecipitated by carbon dioxide; it did not melt below 300° (Found: N, 19·8. $C_{10}H_6O_2N_4Cl_2$ requires N, 19·8%).

The methylalloxan used in the preparation of the 3-methyl*iso*alloxazines was prepared from theobromine by the method of Biltz (*Ber.*, 1912, **45**, 3659). In our experience it is essential to use "AnalaR" stannous chloride in the reduction stage and to keep the reaction solution at −15° for 24 hours in order to induce dimethylalloxantin to crystallize.

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Department of Pharmacology, Oxford. [*Received, December 13th*, 1949.]

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145. *Fucoidin. Part I. The Isolation and Purification of Fucoidin from Brown Seaweeds.*

By E. G. V. Percival and A. G. Ross.

The isolation of the polysaccharide sulphate, fucoidin, from various species of *Phæophyceæ* is described and the results of quantitative analyses are reported.

Fucoidin, the principal polysaccharide sulphate ester of the *Phæophyceæ*, differs from that of the *Rhodophyceæ* in that the main carbohydrate skeleton is founded on fucose instead of on galactose.

Fucoidin which occurs together with mannitol, alginic acid and laminarin, was first described and named by Kylin (*Z. physiol. Chem.*, 1913, **83**, 171; 1915, **94**, 357) who isolated the substance from various species of *Laminaria* and *Fucus* by extraction with dilute acetic acid and subsequent purification. After hydrolysis Kylin isolated phenyl-L-fucosazone and claimed that pentoses were present also in the hydrolysate.

Bird and Haas (*Biochem. J.*, 1931, **25**, 403) obtained fucoidin by soaking fresh fronds of *Laminaria digitata* in water and precipitating a crude sulphate from the viscous extract with ethanol. After suitable treatment a product containing 30·9% of ash (chiefly calcium sulphate) and 30·3% of sulphate was obtained. Since the total sulphate content was approximately double that found in the ash, fucoidin was designated a carbohydrate ethereal sulphate. Bird and Haas (*loc. cit.*) reported the presence of uronic acid (7·3%) in their preparation.

Lunde, Heen, and Öy (*Z. physiol. Chem.*, 1937, **247**, 189) allowed the droplets exuding from freshly-gathered *Laminaria digitata* to fall into ethanol, and, after its purification from boiling ethanol, obtained a specimen with an ash content of 26—30% of which the sulphate content was approximately half the total estimated in the polysaccharide. In this specimen the principal inorganic ion was sodium. Estimations by distillation with hydrochloric acid gave 33—37% of methylpentose, and since this failed to account for more than 80% of the carbo-

hydrate constituents a formula $(R{\cdot}R'{\cdot}O{\cdot}SO_3{\cdot}OM)_n$ was proposed where R is fucose (as $C_6H_{10}O_4$), R' is unknown, and M may be Na, K, $Ca_{0.5}$ or $Mg_{0.5}$.

Another water-soluble polysaccharide closely related to, if not identical with, fucoidin was first isolated from the giant kelp *Macrocystis pyrifera* (Hoagland and Lieb, *J. Biol. Chem.*, 1915, **23**, 287) and shown to contain L-fucose and a high proportion of calcium and sulphate. Further studies by Nelson and Cretcher (*ibid.*, 1931, **94**, 147) revealed that the sulphate existed in the form of ester groupings, and that the only sugar identified after hydrolysis was L-fucose, although contamination with alginates was suspected on the ground of a uronic acid content of 2·6%.

In an attempt to reconcile some of the conflicting views on the nature of fucoidin, specimens have been prepared from *Fucus vesiculosus*, *Fucus spiralis*, *Laminaria cloustoni*, and *Himanthalia lorea*. The method adopted was by extraction with hot water, removal of alginates and proteins with lead acetate, and addition of barium hydroxide. The resulting lead hydroxide–fucoidin complex was then decomposed with dilute sulphuric acid, and the polysaccharide isolated after prolonged dialysis, although several treatments with "Filter Cel" and precipitation from ethanol were necessary before anything approaching a pure product was obtained. The presence of a sulphate ester was confirmed in the usual way for all our

Source.	Fucose, %.	SO_4, %.	Metals, %.	Ca, %.	$[\alpha]_D^{20}$.
F. vesiculosus	37·4	31·7	—	—	−119°
F. spiralis	35·8	32·7	6·4	5·8	−118
L. cloustoni	36·5	33·5	7·1	6·1	−114
F. vesiculosus	41·2	33·6	6·5	—	—
Himanthalia lorea	43·9	32·4	6·9	—	−140

specimens; in contrast to the findings of Lunde *et al.* (*loc. cit.*) the main inorganic ion was found to be calcium, a typical ash analysis giving Ca 25·0, Mg 1·9, Na 1·1, K 0·8, and SO_4 73·2%. The earlier specimens examined contained glucose, presumably owing to the incomplete removal of laminarin. In the Table the results for a number of specimens of fucoidin are set out. Fucose was estimated by the method of Cameron, Ross, and Percival (*J. Soc. Chem. Ind.*, 1948, **67**, 161) although it was found later that slightly higher values were obtained by chromatographic analysis.

Since a calcium fucosan sulphate would give 66·9% of fucose on hydrolysis it appeared that the view held by Lunde had some justification. Nevertheless a prolonged search by various methods, including periodate oxidation of hydrolysis products and chromatographic analysis, failed to reveal the presence of more than small quantities of other sugars. The discrepancy was accounted for when it was realised that despite drying at 40°/0·1 mm. for 18 hours, the polysaccharide stubbornly retained water (9·4%) and ethanol (6%) as revealed by micro-Zerewitinow determinations and by the use of the method of Newman (*J. Pharmacol.*, 1936, **56**, 278) for the determination of ethanol.

This result recalls the observations of Berner (*Ber.*, 1931, **64**, 842) on the difficulty of removing adsorbed ethanol from inulin, and those of Jansen, MacDonnell, and Ward (*Arch. Biochem.*, 1949, **21**, 149) on the retention of ethanol by polygalacturonic esters. In the present instance the attraction for water is probably enhanced by the presence of the sulphate residues.

After making due allowances for the adsorbed solvents, and by chromatographic estimations of the reducing sugars present, the following result was obtained for the most highly purified specimen of *Himanthalea lorea* fucoidin: SO_4, 38·3; metals, 8·2; uronic acid, 3·3; fucose on hydrolysis, 56·7; galactose, 4·1; xylose, 1·5%. A calcium fucosan monosulphate $(C_6H_9O_3.SO_4Ca_{0.5})_n$ would give: SO_4, 39·2; Ca, 8·2; fucose 66·9%.

The simplest interpretation of these results is that the principal constituent of the fucoidin examined is a fucosan monosulphate and that the other constituents arise from adventitious impurities.

Experimental.

Isolation of Crude Fucoidin from Seaweeds.—Samples of crude fucoidin were prepared from *Fucus vesiculosus*, *F. spiralis*, *Laminaria cloustoni*, and *Himanthalea lorea* as follows: For the first specimens, dried ground seaweed (1 kg.) was extracted with hot water (3 l.) for 24 hours at the temperature of a boiling water-bath and the residue removed by filtration through muslin. The extract was treated with lead acetate solution until precipitation of alginates and proteins was complete. After filtration the solution was made just alkaline to phenolphthalein with barium hydroxide, yielding a lead hydroxide–fucoidin complex which was removed and decomposed with dilute sulphuric acid (300 c.c. of 4*N*-acid in 1 l. of water) by shaking overnight, followed by dialysis for a week in a Cellophane bag to remove the acid, filtration, evaporation (40°/15 mm.) to small bulk, and precipitation in alcohol. The resulting solid, which was washed with alcohol and ether and dried over phosphoric oxide in a vacuum,

was buff-coloured and a representative analysis was: fucose (by the method of Cameron, Ross, and Percival, *loc. cit.*), 29·6; SO_4, 27·3%. Yields: *F. vesiculosus*, 23 g.; *F. spiralis*, 18 g.; *L. cloustoni*, 8 g.

Since the determination of fucose required the preliminary hydrolysis of the polysaccharide, the rate of hydrolysis of the sample from *F. vesiculosus* was followed polarimetrically; hydrolysis was complete in 3 hours in 0·5N-sulphuric acid, the rotation rising from $[\alpha]_D^{17}$ −119° to −24°.

Further Purification of Fucoidin.—Dissolution in water, followed by evaporation and reprecipitation in alcohol, did not increase the fucose content but, if the solution in water was set aside overnight with 2% Johns-Manville "Filter Cel" and then filtered and the product was isolated as before, the fucose released on hydrolysis of the sample noted before rose to 35·4% and a second treatment increased this figure to 37·4%, the total sulphate rising to 31·7%. The samples from other species of seaweed gave similar figures when treated in the same way although these operations involved serious loss of material. Sulphate, metals, and $[\alpha]_D$ were also determined (see foregoing Table).

The sample of crude polysaccharide prepared from *Himanthalea lorea* was extracted from freshly gathered, minced seaweed (50 kg.) as before except that, after decomposition of the lead hydroxide precipitate with acid, the mixture was filtered through "Filter Cel" which removed much colouring matter. The fucoidin (190 g.) was separated after concentration and precipitation in alcohol. This product (20 g.) was redissolved in water and treated twice with charcoal (1%; Merck) and "Filter Cel" (2%) at 90° for ½ hour, yielding after filtration and isolation a pure white product (12 g.) containing fucose 42·9%, SO_4 32·4%, ash 22·6%, and metals 0·9%. This sample, which was used for the later analyses unless otherwise stated, was the most highly purified specimen obtainable by this method, two additional treatments giving a product with the same analytical figures and $[\alpha]_D^{18}$ −140° (*c*, 1·0 in water).

Investigation of Other Components of Crude Fucoidin.—Before the fucoidin was obtained from *H. lorea*, some investigations were made into the undetermined portion of the polysaccharide from *F. vesiculosus*.

Estimation of pentose (Marshall and Norris, *Biochem. J.*, 1937, **31**, 1289, 1939) and uronic acid (MacCready, Swenson, and Maclay, *Ind. Eng. Chem. Anal.*, 1946, **18**, 290) gave figures of 3·4% and 6·6% respectively, but no free sugars or methoxyl groups could be detected. Hypoiodite oxidation after hydrolysis, on the other hand, indicated about 20% of sugars as hexose after allowance for fucose, by addition of excess of alkaline hypoiodite and titration of the excess with thiosulphate after storage for 1 hour and acidification. Oxidation experiments using periodic acid were also carried out after preliminary investigations into the oxidation of glucose and rhamnose. On treatment with periodic acid pentoses and hexoses yield 1 molecule of formaldehyde along with formic acid (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476), the formaldehyde being estimated as the dimedon complex (Vorländer, *Z. Analyt. Chem.*, 1929, **77**, 241). In the present case glucose was found to give 0·96 mol. of formaldehyde when treated in admixture with rhamnose, provided that the acetaldehyde formed from the methylpentose was removed by aeration before precipitation with dimedon. The formic acid liberated was also determined by titration after destruction of the excess of periodate with ethylene glycol, glucose giving 4·90 mols. and rhamnose 3·99 mols. of formic acid. When applied to fucoidin, the production of formaldehyde was equivalent to 19·1% of hexose, and that of formic acid after allowance for fucose to 14·8% of hexose.

A sample of fucoidin was hydrolysed and the fucose mainly removed as the phenylmethylhydrazone, the remaining material, after treatment with benzaldehyde (Lüdtke, *Biochem. Z.*, 1929, **212**, 419), being finally obtained as a glass. A small amount of alcohol-insoluble material was shown to be mainly uronic acid whilst the soluble portion contained fucose 5·4% and hexose (by periodate oxidation) 51·9%. This gave glucosazone (m. p. 186°) which yielded phenyl-D-glucosotriazole (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1945, **67**, 939) (m. p. 196—197°, mixed m. p. 193—194°, $[\alpha]_D^{18}$ −80° in pyridine). These results indicate the presence of glucose since it was found impossible to obtain mannose phenylhydrazone under conditions in which a control mannose solution reacted readily. Estimation of the glucose by the Somogyi micro-copper method (*J. Biol. Chem.*, 1945, **160**, 61) before and after incubation with yeast at 37° (Harding and Selby, *Biochem. J.*, 1931, **25**, 1815) indicated the presence of 15·8% of glucose in the glass along with a similar amount of another reducing sugar, not absorbed by yeast, which was not identified.

Properties of Fucoidin as a Free Acid.—Freshly prepared fucoidin solution (0·2%) had a pH value of 6·1 which fell to 4·0 on storage for 1 week owing to autohydrolysis. Fucoidin (0·35 g.) was dissolved in water (150 c.c.), and the solution titrated electrometrically with sodium hydroxide (0·01N.) with a platinum–quinhydrone–N-calomel cell. After titration to a pH of 7·26, the calculated amount of oxalic acid necessary to precipitate exactly the calcium present was added and the titration of the free acid continued using sodium hydroxide (0·1N.). The results in the following table indicate the presence of a strong acid.

C.c. of NaOH (0·1045N.) added ...	—	1·0	3·0	5·0	6·0	7·0	9·0	9·5	9·6	9·7
pH	3·72	3·74	3·91	4·45	4·63	4·96	5·79	6·84	7·16	7·26

Further Analyses of the Purest Fucoidin from H. lorea.—All analyses were carried out on samples dried at 40°/0·1 mm. for 16 hours. This sample contained fucose 43·9% and SO_4 32·4%. Quantitative paper chromatographic analysis (Flood, Hirst, and Jones, *J.*, 1948, 1679) on this material, after hydrolysis, gave fucose 48·4%, which is slightly higher than that obtained by the volumetric estimation. Fucoidin (1·247 g.) was hydrolysed with sulphuric acid (100 c.c.; N.) and neutralised, and the free sugars were obtained as a glass, all the operations being carried out as far as possible quantitatively. The glassy product (0·755 g. or 60·5%) had $[\alpha]_D^{18}$ −54·8 (*c*, 1·26 in water), fucose 75·0%, sulphate as calcium sulphate 7·8%, and sulphated ash 7·2%. A quantitative paper chromatogram on the glass gave fucose 79·1% and galactose 7·2%, representing 48·0% and 4·4% respectively calculated on the polysaccharide. Development of a chromatogram with aniline oxalate solution confirmed the presence of hexose (brown spot) and also indicated a small quantity of a pentose (pink spot) corresponding to

xylose. A second quantitative determination using more material was carried out and gave galactose amounting to 5·8% and xylose 2·2% of the glass.

The analytical figures to date on the polysaccharide were fucose 48·0%, galactose 3·5%, xylose 1·3%, uronic acid 2·8%, sulphate 32·4%, and metals 6·9%. Calculation of these figures to anhydro-sugars, etc., as in the polysaccharide showed that about 15% remained to be accounted for.

Alcohol determinations were carried out by the method of Newman (*J. Pharmacol.*, 1936, **58**, 278) on samples dried for 18 hours at 40°/0·1 mm. The alcohol is removed from the sample by evacuation after dissolution in water and addition of anhydrous sodium sulphate, and is absorbed in acid dichromate solution; the excess of dichromate is then titrated with sodium thiosulphate in the presence of potassium iodide. Found: adsorbed alcohol 6·0% (average of three determinations). Adsorbed water was also investigated and determined by means of the Zerewitinow reaction (*Ber.*, 1907, **40**, 2033) modified to the micro-determination of active hydrogen (Flaschenträger, *Z. physiol. Chem.*, 1925, **146**, 219; Pregl-Grant, "Quantitative Organic Micro-analysis," 4th Edn., 1945), allowance being made for the active hydrogen in the ethanol in the polysaccharide. It was found that methane was produced equivalent to 9·5% of water in the polysaccharide. The possibility of other reactions taking place was negatived by a similar determination on starch with a known moisture content of 12·1% (Found: water 12·7%). By weighing a supposedly dry sample of fucoidin at intervals after storage in an atmosphere of 60% relative humidity, it was found that after 1 day the moisture content increased by 17% and, after 6 days, by 26%, showing that intensive drying before analysis is necessary and confirming the possibility of fucoidin's high power of retaining water after being dried by the normal methods.

The addition of water and alcohol to the previous analytical figures brings the total percentage accounted for to 99·3%.

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KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, December 13th*, 1949.]

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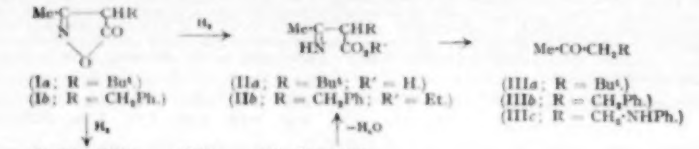
146. *The Hydrogenation of Some* iso*Oxazolones.*

By G. SHAW.

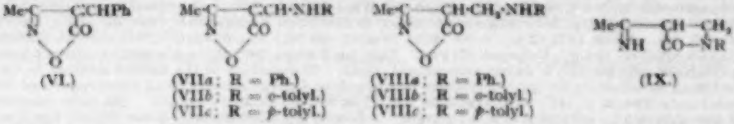
Hydrogenation of 4-benzylidene-3-methyl- and 3-methyl-4-anilinomethylene-*iso*oxazolones using a palladium catalyst affords the 4-benzyl- and 4-anilinomethyl-*iso*oxazolones. When a platinum catalyst is used in moist solvents, disruption of the *iso*oxazolone nucleus occurs and linear ketones are obtained; in anhydrous ethanol hydrogenation of the 4-benzylidene- and 4-benzyl-*iso*oxazolones affords ethyl α-benzylacetoacetate, suggesting the formation of a reactive anhydride-like substance, possibly an *iso*oxazolidone (IV). Hydrogenation of propiophenone oxime acetate affords the corresponding acylketimine. Oxidation of propiophenone acetylimine with potassium permanganate in acetone, in an attempt to reverse the last-mentioned reaction, gives *N*-acetylbenzamide.

IT has been shown recently (Panizzi, *Gazzetta*, 1946, **76**, 44) that hydrogenation of 3-methyl-4-*tert.*-butyl*iso*oxazol-5-one (I*a*), using a large excess of platinum as catalyst and acetic acid as solvent, affords *tert.*-butylacetone (III*a*); Panizzi points out the unexpected lability of oxygen in the *iso*oxazolone nucleus and suggests that ketone formation is preceded by formation of 3-imino-α-*tert.*-butylbutyric acid (II*a*). Evidence is now presented which suggests that hydrogenation of the *iso*oxazolone system produces a reactive anhydride-like substance, possibly the *iso*oxazolidone (IV) which may yield (II) *via* the hydroxylamine derivative (V).



Hydrogenation of 4-benzylidene-3-methyl*iso*oxazol-5-one (VI) over 5% palladium–charcoal in ethanol or ethyl acetate at room temperature resulted in the absorption of only 1 mole of hydrogen and formation of 4-benzyl-3-methyl*iso*oxazol-5-one (I*b*). Hydrogenation of the basic arylaminomethylene*iso*oxazolones (VII*a*—*c*) under the same conditions afforded quantit-

ative yields of the corresponding *arylaminomethyl*isoo*xazolones* (VIIIa—c) which readily formed *picrates*.

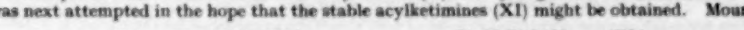


(VI.) (VIIa; R = Ph.) (VIIb; R = *o*-tolyl.) (VIIc; R = *p*-tolyl.) (VIIIa; R = Ph.) (VIIIb; R = *o*-tolyl.) (VIIIc; R = *p*-tolyl.) (IX.)

It soon appeared that Adams's platinum catalyst was required for the disruption of the *iso*oxazolone nucleus: when thus reduced in ethanol or ethyl acetate, (VI) absorbed 2 moles of hydrogen affording ammonia and an oil consisting largely of 4-phenylbutan-2-one (IIIb). Under the same conditions 4-benzyl-3-methyl*iso*oxazol-5-one (Ib) absorbed 1 mole of hydrogen and gave the same products. In these experiments no special precautions were taken to exclude moisture. When (Ib) was reduced with hydrogen–platinum in absolute ethanol under anhydrous conditions 1 mole of hydrogen was absorbed but no ammonia was formed, and from the reaction mixture was isolated ethyl α-benzylacetoacetate and a base which was rapidly hydrolysed to the keto-ester and was probably its imine (IIb). The identity of the keto-ester was confirmed by conversion by warm concentrated sulphuric acid into 1-methylindene-2-carboxylic acid (von Pechmann, *Ber.*, 1883, **16**, 516; Roser, *Annalen*, 1888, **247**, 157). The keto-ester was also obtained by reduction of (VI) under anhydrous conditions in absolute ethanol, but neither (VI) nor (Ib) showed evidence of reaction with ethanol at room temperature. Hydrogenation of 3-methyl-4-anilinomethylene*iso*oxazol-5-one (VIIa) in moist solvents afforded ammonia and 4-anilinobutan-2-one (IIIc), but in anhydrous solvents a viscous liquid was obtained which could not be satisfactorily identified; work in this direction is being pursued to ascertain the possibility of formation of an azetidinone or β-lactam (IX) which might conceivably arise by rearrangement of the hypothetical *iso*oxazolidone (IV; R = CH_2·NHPh).

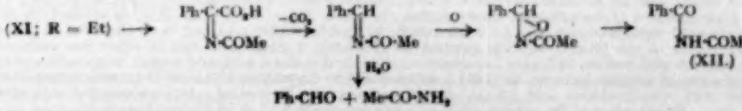
The isolation of ethyl α-benzylacetoacetate by reduction of (Ib) and (VI) in ethanol implies the intermediate formation of an anhydride-like substance capable of combining with the solvent and this substance is postulated provisionally as the *iso*oxazolidone (IV). Attempts to isolate such a compound by carrying out the reduction in anhydrous ethyl acetate were unsuccessful, a viscous oil being obtained from which benzylacetone alone could be isolated.

The system $-C(:N\cdot O\cdot CO-)$ exists in the acyloximes (X) and hydrogenation of these substances was next attempted in the hope that the stable acylketimines (XI) might be obtained. Moureu



(X.) (XI.)

and Mignonac (*Compt. rend.*, 1913, **156**, 1805; 1920, **170**, 1354) showed that reduction of oximes with hydrogen–platinum afforded the ketimines and prepared a number of acylketimines by acylation of these substances and also by an independent method. In presence of platinum in ethanol propiophenone oxime acetate (X; R = Et) absorbed 1 mole of hydrogen during 4 hours, to afford propiophenone *N*-acetylimine (XI; R = Et), identical with a sample prepared from phenylmagnesium bromide, propionitrile, and acetyl chloride (Moureu and Mignonac, *loc. cit.*). Hydrogenation of acetophenone oxime acetate (X; R = Me) under the same conditions afforded an oil which was presumably the ketimine (XI; R = Me) since it gave acetophenone, ammonia, and acetic acid when hydrolysed. In an attempt to reverse the latter reaction, propiophenone *N*-acetylimine (XI; R = Et) was treated with potassium permanganate in acetone, but, instead of the expected oxime acetate, *N*-acetylbenzamide (XII) was obtained in good yield, together with a small amount of benzaldehyde. This suggests that the oxidation may proceed according to the scheme:



Experimental.

Hydrogenations were carried out at room temperature and atmospheric pressure; the recorded volumes of hydrogen refer to N.T.P.

Hydrogenation of 4-*Benzylidene*-3-*methyl*iso*oxazol*-5-*one* (VI).—The *iso*oxazolone (1 g.; Dains and

Griffin, *J. Amer. Chem. Soc.*, 1913, **35**, 959) in 90—95% ethanol (30 ml.) was reduced with hydrogen and 5% palladium–charcoal (0·1 g.), hydrogen (131 ml. Calc. for 1 mol., 120 ml.) being absorbed during 1 hour. Evaporation of the filtered solution *in vacuo* gave an oil which partly crystallised. 4-Benzyl-3-methyl-*iso*oxazol-5-one (*Ib*) (0·2 g.) separated from benzene as needles, m. p. 106°, undepressed when mixed with an authentic specimen, m. p. 107°, prepared according to Schiff and Viciana (*Ber.*, 1897, **30**, 1161; *Gazzetta*, 1897, **27**, 73). When (VI) (2 g.) in 90—95% ethanol (30 ml.) was reduced with hydrogen–platinum (Adams's catalyst) (0·1 g.), hydrogen (244 ml. Calc. for 2 mols., 240 ml.) was absorbed during 4 hours; the resultant solution had a strong ammoniacal odour. Evaporation of the filtered solution *in vacuo* afforded an oil which readily gave crystalline benzylacetone semicarbazone (1·3 g.) which separated from ethanol as needles, m. p. 142°, undepressed on admixture with an authentic sample. The same compound was also obtained by reduction in ethyl acetate. 4-Benzyl-3-methyl*iso*oxazol-5-one (*Ib*) did not absorb hydrogen in the presence of palladium, but in presence of a platinum catalyst 1 mole of hydrogen was absorbed with formation of ammonia and benzylacetone. (VI) (2 g.) in anhydrous ethanol (30 ml.) was reduced with hydrogen–platinum, with exclusion of moisture; hydrogen (245 ml. Calc. for 1 mol., 240 ml.) was absorbed during 3 hours and the solution became slightly alkaline but there was no odour of ammonia. Evaporation of the filtered solution *in vacuo* gave an oil (1·9 g.) which gave a purple colour with alcoholic ferric chloride. The oil in ether (20 ml.) was extracted successively with 2% sodium hydrogen carbonate solution (2 × 10 ml.), 2% hydrochloric acid (2 × 10 ml.), and water (10 ml.). Evaporation of the dried solution afforded ethyl α-benzylacetoacetate (1·3 g.), b. p. 165—169°/12 mm. (Leucha, *Ber.*, 1911, **44**, 1510, gives b. p. 164—165°/12 mm.). The oil (0·5 g.) and concentrated sulphuric acid (3 ml.) were heated on a water-bath for 10 minutes, then cooled, and poured into ice-water (100 ml.); 1-methylindene-2-carboxylic acid (0·25 g.) was obtained as a white precipitate, which separated from ethanol as needles, m. p. 200°, undepressed when mixed with an authentic specimen, m. p. 200°, prepared from ethyl α-benzylacetoacetate and sulphuric acid (von Pechmann, *loc. cit.*; Roser, *loc. cit.*). Acidification of the sodium hydrogen carbonate solution, extraction with ether, and evaporation afforded only a trace of gum, indicating absence of acid. The acid extract when kept for a few hours deposited an oil (0·2 g.) (insoluble in sodium hydrogen carbonate solution), which afforded 1-methylindene-2-carboxylic acid when treated with sulphuric acid and was probably ethyl α-benzylacetoacetate, the basic precursor being presumably ethyl α-benzylacetimidoacetate (*IIb*).

3-*Methyl*-4-*anilinomethylisooxazol-5-one* (VIIIa).—3-Methyl-4-anilinomethylene*iso*oxazol-5-one (VIIa) (1 g.; Dains and Griffin, *loc. cit.*) in 90—95% ethanol (30 ml.) was reduced in presence of 5% palladium–charcoal (0·1 g.), hydrogen (110 ml. Calc. for 1 mol., 111 ml.) being absorbed in 2 hours. Evaporation of the filtered solution *in vacuo* gave 3-*methyl*-4-*anilinomethylisooxazol-5-one dihydrate* as a pale yellow solid (1 g.) which separated from water as fine pale yellow needles, m. p. 101—102° (decomp.) (Found : N, 11·6. $C_{11}H_{14}O_3N_2.2H_2O$ requires N, 11·63%). This lost water when heated at 50°/1 mm. for 1 hour to give the anhydrous *iso*oxazolone as a very pale yellow powder, m. p. 150°; the anhydrous material was extremely deliquescent (rapidly reverting to the dihydrate in moist air) and could not be recrystallised satisfactorily, but when it, or the dihydrate, was added to a saturated solution of picric acid in ethanol, the *picrate* was precipitated as a yellow solid which separated from ethanol as prisms, m. p. 167—168° (decomp.) (Found : N, 16·3. $C_{17}H_{16}O_{10}N_6$ requires N, 16·15%). 3-Methyl-4-anilino-methylene*iso*oxazol-5-one (2 g.) in 90—95% ethanol (40 ml.) was reduced with platinum (0·1 g.), hydrogen (225 ml. Calc. for 2 mols., 222 ml.) being absorbed in 3 hours. Evaporation of the filtered solution (which possessed an ammoniacal odour) *in vacuo* gave almost colourless 4-anilinobutan-2-one, b. p. 149—155°/14 mm. (1·5 g.), which became brown in the air (Found : N, 8·4. Calc. for $C_{10}H_{13}ON$: N, 8·6%). Bayer and Co. (*Zentr.*, 1913, II, 1832) give b. p. 140—145°/10 mm.

3-*Methyl*-4-*p-toluidinomethylisooxazol-5-one* (VIIIc).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (VIIc) (1 g.), when reduced with hydrogen–palladium as above, afforded 3-*methyl*-4-*p*-*toluidino-methyl*-*isooxazol-5-one* (0·95 g.) which separated from water as fine, very pale yellow needles, m. p. 181—182° (decomp.) (Found : N, 12·7. $C_{12}H_{14}O_2N_2$ requires N, 12·8%). The *picrate* crystallised from ethanol as prisms, m. p. 167—169° (decomp.) (Found : N, 15·4. $C_{18}H_{17}O_9N_5$ requires N, 15·65%).

3-*Methyl*-4-*o-toluidinomethylisooxazol-5-one* (VIIIb).—This *product* separated from water as fine pale yellow needles, m. p. 163—164° (decomp.) (Found : N, 12·65%). The *picrate* separated from ethanol as yellow prisms, m. p. 150° (decomp.) (Found : N, 15·45%).

Propiophenone Oxime Acetate (X; R = Et).—Propiophenone oxime (13·5 g.) and acetic anhydride (15 ml.) were heated on the water-bath for 3 hours. Evaporation of the solution *in vacuo* gave an oil which soon crystallised; *propiophenone oxime acetate* (10·5 g.) separated as needles (from light petroleum), m. p. 57° (Found : N, 7·25. $C_{11}H_{13}O_2N$ requires N, 7·35%). The acetate (5 g.) was reduced with hydrogen and platinum (0·2 g.) in ethanol (100 ml.) until 1 mole of hydrogen (585 ml.) had been absorbed, this requiring 5 hours. The filtered solution was evaporated *in vacuo* to afford a pale brown oil, which partly crystallised on being kept overnight. The crystals (1·4 g., 31%) were separated from oil by spreading the mixture over a porous tile, and recrystallised from water as needles, m. p. 125°, undepressed when mixed with an authentic sample of propiophenone *N*-acetylimine (XI; R = Et), m. p. 126°.

Hydrogenation of Acetophenone Oxime Acetate (X; R = Me).—The acetate (2 g.) in ethanol (30 ml.) was reduced with platinum (0·1 g.) until 1 mole of hydrogen (252 ml.) had been absorbed (4 hours). Evaporation of the filtered solution gave an oil (1·9 g.). A solution of this in ether was extracted successively with sodium hydrogen carbonate solution, hydrochloric acid, and water; evaporation of the dried ethereal solution gave an oil (1·3 g.) which failed to crystallise. The oil (1 g.) was boiled under reflux with *N*-hydrochloric acid (10 ml.) for 30 minutes, and the cooled solution extracted with ether (20 ml.). Evaporation of the extract afforded acetophenone (0·5 g.) (2 : 4-dinitrophenylhydrazone, m. p. 248°, undepressed when mixed with an authentic specimen, m. p. 250°). The aqueous solution was evaporated to a small volume and made alkaline with *N*-sodium hydroxide, whereupon ammonia was evolved; neutralisation of the solution and addition of ferric chloride produced a red colour, and boiling the mixture precipitated basic ferric acetate.

Oxidation of Propiophenone N-Acetylimine (XI; R = Et).—A solution of the acylketimine (1 g.) in acetone (100 ml.) was boiled under reflux, and solid potassium permanganate added until a lasting pink

colour was obtained (about 3 g. were required). The solution was filtered, the filtrate decolorised with sulphur dioxide and re-filtered, and the filtrate evaporated to dryness *in vacuo*, to yield crystalline *N*-acetylbenzamide (0·8 g.) which separated from water as laths, m. p. 116°, undepressed when mixed with an authentic specimen, m. p. 116° (Titherley and Holden, *J.*, 1912, **101**, 1880). The filtrate from the above crystallisation had an odour of benzaldehyde and gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235°, thereof.

TECHNICAL COLLEGE, SYDNEY, N.S.W., AUSTRALIA. [*Received, October 25th*, 1949.]

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147. *Crossed Reaction Chains in Oxidation by Molecular Oxygen. Part I. Oxidation of Hydrocarbons in Aldehyde–Air Mixtures.*

By N. J. H. SMALL and A. R. UBBELOHDE.

One theory of hydrocarbon oxidation assumes that the reaction chain

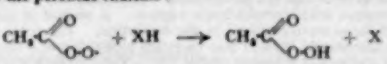
$$R + O_2 \longrightarrow RO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RO_2 + RH \longrightarrow RO{\cdot}OH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

is closely similar whether R is an alkyl radical in the oxidation of hydrocarbons, or an acyl radical in the oxidation of aldehydes.

To test how far the oxidation chains for these two molecular species can in fact "cross," small proportions of paraffins, olefins, benzene, and hydrogen have been added to an acetaldehyde–air mixture undergoing vigorous oxidation around 150—200°. These added molecules were found either to be substantially inert, or to act as inhibitors for the oxidation of the acetaldehyde.

The conclusion is that the oxidation chains of the hydrocarbon tested cannot "cross" freely with those for acetaldehyde, at the temperature of the experiment. When the added molecules act as inhibitors for the oxidation of acetaldehyde, they may do so by donation of hydrogen atoms to the peroxide radicals :



but the resulting X radicals do not themselves continue long oxidation chains under the conditions used. The inhibiting action of hydrogen may also be caused by its deactivating "energy chains" by facilitating the exchange of vibrational energy.

THE close relation between the oxidation mechanism of gaseous aldehydes and that of gaseous paraffins has been noted by various authors, and has been used to elucidate some of the steps in hydrocarbon oxidation (Ubbelohde, *Proc. Roy. Soc., A*, 1935, **152**, 354, 378; Lewis and Von Elbe, "Flames, Combustion and Explosions of Gases," Cambridge, 1938).

One of the outstanding difficulties in substantiating the details of a scheme of oxidation for gaseous hydrocarbons is that the minimum temperature at which reaction can conveniently be observed at ordinary pressures is around 250°. At this temperature, labile reaction products such as hydroperoxides, whose constitution is particularly significant, are frequently too short-lived for identification except by special techniques (Egerton, Llewellyn Smith, and Ubbelohde, *Phil. Trans.*, 1935, **234**, 433; Ubbelohde, Drinkwater, and Egerton, *Proc. Roy. Soc.*, 1936, **153**, No. 878, 103). The guiding idea in the researches to be described is to discover which of the numerous reaction steps in the oxidation of hydrocarbons imposes the use of temperatures as high as 250°. In particular, the aim was to investigate how far the reaction rate was controlled by the postulated initial attack on the hydrocarbon

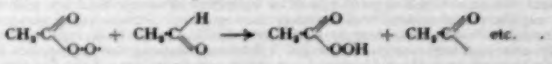
$$X + RH \longrightarrow XH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

where X may be any third body; in the main oxidation chain X is a peroxide radical (cf. Ubbelohde *et al.*, *locc. cit.*), *i.e.*,

$$R + O_2 \longrightarrow RO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RO_2 + RH \longrightarrow RO{\cdot}OH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The experimental principle employed was to bombard the RH molecule with a large number of aldehyde peroxide radicals, at a temperature where the reaction



is proceeding freely, and to investigate :

(*a*) Whether the result of the attack was to start *hydrocarbon* oxidation chains according to (1) and (2) above;

(*b*) Failing the establishment of such chains, whether there was any evidence for the formation of alkyl radicals under the initial bombardment of hydrocarbon by aldehyde peroxide radicals, according to reaction (*A*), but without extensive sequences of (1) and (2); and

(*c*) Failing either (*a*) or (*b*), whether there was any evidence of chemical crossing of reaction chains at the temperature of the experiment.

Possibility (*a*) would have the great practical advantage of permitting the controlled oxidation of hydrocarbons in the vapour phase at much lower temperatures than usual; this could lead to interesting and valuable oxidation intermediates.

Possibility (*b*) would be of very considerable theoretical interest, as indicating new facts about the kinetic characteristics of the oxidation steps for paraffins. The yields of interesting oxidation intermediates would, however, be much smaller since proportionally many fewer paraffin molecules would enter into reaction for each R radical formed according to (*A*).

Finally, possibility (*c*) would imply the need for very considerable activation energy, even for reaction (*A*).

As is discussed below, the main conclusion was that none of the hydrogen compounds so far exposed to bombardment by acetaldehyde peroxide radicals appears to undergo reaction according to (*a*). Heptane, hydrogen, and hex-1-ene give definite evidence of following course (*b*). This has theoretical as well as practical implications which are further detailed below.

Experimental.

Experimental Procedure.—The main lines of experimental procedure can be summarised by reference to Fig. 1. *A*—*B* is a Pyrex reaction tube, 50 cm. long, of internal diameter 4·5 cm., wound with nichrome wire and lagging, and heated electrically so as to maintain the gas flowing through it at any temperature up to approx. 360°. At the inner ends of *a*, *b*, *c*, broken glass fragments and glass wool serve to produce turbulence so as to mix the gas streams. Normally one of these is pure nitrogen charged to a calculated partial pressure with acetaldehyde vapour. A second is air, which could be used to carry the XH molecules if these were required in the oxidation. The total flow in mols./sec. was not appreciably affected when the second stream was carrying molecules of a compound XH (see Table I). For mixing in hydrogen or additional nitrogen (Table I *b*), a third stream was introduced as indicated in Fig. 1 (*c*).

Table I.

	Mixture.	CH_3·CHO.	XH.	O_2.	N_2.	Total rate of flow.	Temp. of steep rise of oxidation rate.
a.	CH_3·CHO/(ref. O_2/N_2 mixture) ...	0·267	—	0·0937	0·803	1·164	150°
b.	.. + N_2 *	0·267	0·142 *	0·0937	0·803	1·306	190
c.	.. + C_6H_6	0·267	0·0982	0·0937	0·803	1·262	190
d.	.. + C_6H_{14}	0·267	0·142	0·0937	0·803	1·306	190
e.	.. + C_7H_{16}	0·267	0·100	0·0937	0·803	1·264	200
f.	.. + H_2	0·267	0·150	0·0937	0·803	1·314	210
g.	.. + unsaturated	0·267	0·125	0·0937	0·803	1·289	*ca.* 200

* Additional N_2 in this mixture matches approx. the amount of XH in mixtures *c* to *g*.
Figures are in 10^{-6} g.-mols./sec.

By this means a mixture of acetaldehyde and (nitrogen + XH) in approximately constant molar proportions flowed through the reaction tube at constant velocity. The aim was to maintain substantially constant conditions for the aldehyde oxidation, except in so far as these were modified by the crossing of the aldehyde reaction chains with any reactions involving XH.

At *B* the condensing system was maintained at the temperature of liquid oxygen, the cold finger shown in Fig. 1 being cooled by means of carbon dioxide and alcohol. As required, this condensation vessel could be rapidly interchanged with similar vessels, so as to permit collection of a series of samples without any interruption in the reaction flow. The products were allowed to melt and were analysed as described below.

The reactions and the melting of the reaction products were carried out behind protective screens, since when oxidation is extensive very considerable yields of peroxide might be formed. Actually only mild ignitions were observed from time to time when combustion was in progress.

A cross piece fitted with quartz windows was also provided in the reaction system near *A*. This was for use in experiments on photochemical initiation described in subsequent publications, but will not be referred to again in the present paper.

Experimental Details.—Gases were taken from cylinders of compressed air and nitrogen at rates controlled by capillary flow meters with mercury manometers. Stream (*a*) (approx. 10 c.c./sec.) was nitrogen saturated at 0° with acetaldehyde vapour and shielded from strong light. Stream (*b*) consisted of air normally saturated with various molecules XH by maintaining the appropriate liquid in a pair of carburettors at the calculated temperatures. A third stream (*c*) was used for the compositions (*b*) and (*f*) in Table I. This gave approximately constant composition, as is shown in Table I.

Details of the carburettors are illustrated in Fig. 2. Tests showed that with carburettors in series no increase in their number beyond two further increased the content of the gas in aldehyde or in XH, *i.e.*, saturation was effectively attained.

Temperature control in the baths around the carburettors was by an immersion heater regulated by a Sunvic control.

Materials.—Acetaldehyde. This was prepared by distilling paraldehyde with dilute sulphuric acid as required, using a current of nitrogen to protect it from oxidation.

Benzene, f. p. 5·48°. This was prepared by repeated crystallisation of "AnalaR" benzene, thiophen-free. It was used with the carburettor vessel at 50·5° to give a partial pressure of 280 mm.

n-Heptane. This was prepared by fractionating commercial heptane and collecting the cut of b. p. 95·5—97°. Before fractionation unsaturated hydrocarbons were carefully removed on account of their suspected action as inhibitors. The crude heptane was stored over fuming oleum for about a week with occasional shaking. It was then repeatedly washed with strong potassium hydroxide solution and then with water, and dried (Na_2SO_4) for 24 hours. Carburettors at 68° gave $p = 280$ mm.

n-Hexane. This was prepared in the same way as *n*-heptane. The final cut had b. p. 67·5—68·5°. Both fractionations were carried out in nitrogen. Carburettors at 41° gave a partial pressure of 280 mm.

n-Hex-1-ene. This was prepared by dehydrating *n*-hexyl alcohol by the procedure recommended in *Org. Synth.*, Vol. I, p. 421. The fraction of commercial *n*-hexyl alcohol, b. p. 155·2—156·0°, was dehydrated with 50% aqueous sulphuric acid, and the hydrocarbon was repeatedly washed with concentrated sodium hydroxide solution and then refluxed for 24 hours with two successive batches of 20% aqueous sodium hydroxide solution to remove any trace of sulphur compounds.

Final drying (Na_2SO_4) and fractionation through a column gave a cut of b. p. 61—64°. No trace of sulphur compounds was detected in the product. This material was mixed with twice its volume of *n*-hexane and used with carburettors at 41° to give $p = 280$ mm.

FIG. 1.

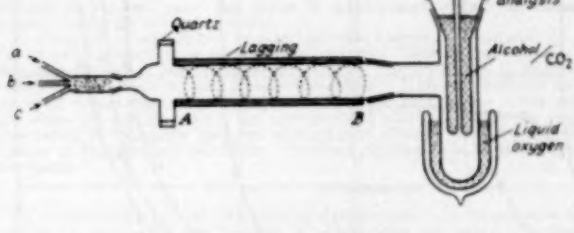


FIG. 2.

Combustion apparatus and vapourisers.

Hydrogen. Taken from cylinders, this was used without further purification. Its rate of flow was determined by a separate flowmeter and was adjusted to a value such that the amount of hydrogen passing through the combustion tube was comparable to the concentration of molecules XH used in previous experiments.

Preparation of the Reaction Vessel.—Before each run, the reaction vessel was cleaned with hot nitrating acid at about 80°, then with abundant distilled water, and finally dried with filtered air. The temperature was measured by a thermometer reading to 360° ± 0·5° and wholly encased in a Pyrex tube which was likewise cleaned with nitrating acid etc. before each run. The degree of reproducibility thus achieved was good, as can be inferred, for example, from the results on the oxidation of pure acetaldehyde (Figs. 3 and 4).

Collection and Analysis of Products.—Only summarised results will be given in the present paper.

The amounts of acetaldehyde, XH, and oxygen used in a run were determined by analysis and checked from the amounts remaining in the calibrated carburettors and the volumes of gases used. The gases flowing past the cooled surfaces were normally stripped of all except permanent gases and possibly some carbon dioxide. Completeness of condensation was verified, for example, by the obtaining of negative tests for acetaldehyde and formaldehyde during the progress of a run. When the percentage content of carbon dioxide was required, samples of exit gases were collected without the condensing system in place. Exit gases were analysed by a "fountain" gas-analysis apparatus which need not be detailed here.

The treatment of the melted condensate was as follows: As a precautionary measure, 25 c.c. of distilled water were first added, to dilute any peroxides formed. When hydrocarbon had been added the condensate separated into two layers. The hydrocarbon layer was shaken 4—5 times with water, and the washings were added to the aqueous layer. The whole aqueous product was made up as a standard solution which could be titrated for peroxide, acid, and aldehyde content (see below).

In the case of *n*-heptane, recovered hydrocarbon, after being scrubbed with water, was carefully

fractionated to obtain a preliminary idea of the fate of the molecules of XH which had reacted. Not more than 1% of the *n*-heptane had given rise to oxidation products of comparable molecular weight.

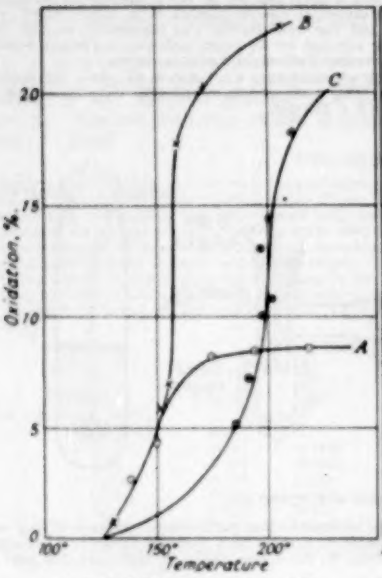
More detailed investigation of what happens to those molecules of XH which are attacked whilst passing through the reacting aldehyde–oxygen system requires special techniques, in view of the small amounts involved. This is being described in subsequent papers.

Fine needle-like crystals were also isolated from the residues of fractionation. Qualitative tests showed this to be a polymerisation product of acetaldehyde. That it is probably metaldehyde seems to be confirmed (i) by m. p. *ca.* 125° and (ii) by the fact that heating them with a drop of dilute acid yielded acetaldehyde.

The aqueous layer contained unchanged acetaldehyde, formaldehyde, peroxides, and acids (chiefly acetic and peracetic).

FIG. 3.

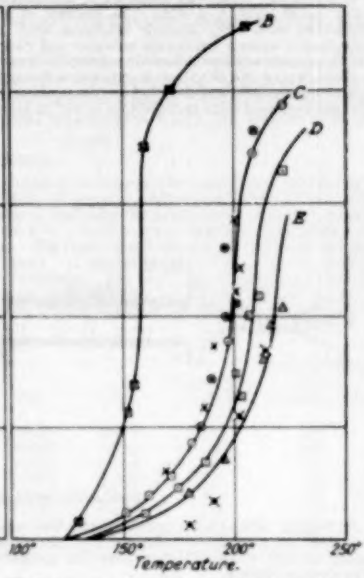
Effect of aldehyde/O_2/N_2 ratio on the critical oxidation temperature of acetaldehyde.



× *Fuel*/O_2/N_2 *ratio* = 2·8 : 1 : 8·57.
○ *Fuel*/O_2/N_2 *ratio* = 1 : 1 : 6.
⊕ *Fuel*/O_2/N_2 *ratio* = 2·8 : 1 : 8·57 + *added* N_2.

FIG. 4.

Effect of added molecules on the critical oxidation temperature of an aldehyde/O_2/N_2 mixture 2·8 : 1 : 8·57.



⊠ *Reference mixture Ald.*/O_2/N_2 2·8 : 1 : 8·57.
× " " + *added benzene.*
⊗ " " + *added nitrogen.*
○ " " + *added hexane.*
⊡ " " + *added heptane.*
△ " " + *added hydrogen.*
✖ " " + *unsaturated.*

The peroxides were determined by filling conical flasks, containing aliquot portions of the scrubbing water with carbon dioxide, adding potassium iodide and dilute sulphuric acid, and allowing reaction to proceed for 2 minutes before titration with standard sodium thiosulphate solution. Prompt analysis of the peroxides was necessary after the melting of the condensate, since the concentration of peroxides in the scrubbing liquor decayed to one-half in *ca.* 15 minutes. This decay could be delayed by addition of free acid to the scrubbing water. In the experimental results given below, the data for peroxides were generally obtained within 2—3 minutes of melting of the condensate. They are believed to be fairly close to the initial concentrations present, unless the decay on condensation or on melting is much more rapid than the average estimated for the samples made up.

Acids formed were titrated with *N*-sodium hydroxide (phenolphthalein).

The total aldehyde content was analysed by means of sodium sulphite (cf. Walker, "Formaldehyde," 1944, p. 257) using thymolphthalein as indicator and titrating the alkali produced with *N*-sulphuric acid.

Where required, formaldehyde was determined separately by the method used by Egerton, Smith,

and Ubbelohde (*loc. cit.*). Addition of an equal volume of 10% sulphuric acid to the test solution suppresses the reaction of the higher aldehydes with Schiff's reagent and makes it specific for the determination of formaldehyde. The acetaldehyde which is present in appreciably greater amounts gives an immediate colour, but this fades in ½ hour, whereas that due to formaldehyde does not fade in 12 hours.

During the analysis the purple tint due to the formaldehyde present was compared colorimetrically with that produced by a standard solution, and the result is included in the table below.

Results.—(a) *Oxidation of pure n-heptane and pure n-hexane.* In confirmation of previous results, experiments which need not be recorded in detail showed that when various mixtures of these paraffins with oxygen and nitrogen in proportions similar to those in Table I were passed through the apparatus without acetaldehyde, the minimum temperature at which appreciable oxidation could be detected under the most favourable conditions was 250°. Products included peroxides and much formaldehyde.

(b) *Formation of acids and peroxides.* With acetaldehyde mixtures, the dominant reaction either alone or in the presence of XH was in all cases the oxidation of the acetaldehyde. Curves in Figs. 3 and 4 show plots of the aldehyde oxidised to peroxide and acid. The sum of the g.-equivs. of these two constituents produced under different conditions is expressed as a percentage of the acetaldehyde originally present in the reaction mixture. Smooth plots are obtained with a steep rise at a critical temperature which depends on the mixture used and on any inhibiting effects due to XH. For convenience these temperatures are listed in the last column of Table I.

(c) *Other oxidation products of acetaldehyde.* Representative gas analyses are given in Table II. It will be observed that at the temperature of the experiment both carbon monoxide and dioxide are

TABLE II.

Representative gas analysis (reaction tube, 200°. Mixture Ia).

Material.	Supplied.	Recovered.	Material.	Supplied.	Recovered.
Acetaldehyde	1·23 g.-equiv.	0·155 g.-equivs.	Formaldehyde	—	0·022 g.-equivs.
Oxygen	0·241 g.-equivs.	0·029 g.-mols.	Peroxide	—	0·085 „
CO_2	—	0·0156 „	Acid	—	0·135 „
CO	—	0·029 „			

detectable in the exit gases, the former in greater quantity. Other oxidation products of higher molecular weight are referred to above.

(d) *Oxidation of heptaldehyde by acetyl peroxide radicals.* As an addition to determination of the effect of added molecules on acetaldehyde oxidation (Table I), heptaldehyde was introduced into an aldehyde oxidation at 200° (carburettors at 104°). About half of it could be recovered under these conditions, the remainder being apparently oxidised. If the formation of the corresponding aldehyde is an early step in hydrocarbon combustion, then the observations in the previous paragraph suggest that, when the paraffin reacts, the corresponding aldehyde should be recoverable. A preliminary fractionation of *n*-heptane collected after passage through the oxidising aldehyde system gave no evidence of heptaldehyde formation. Further comment is reserved until larger quantities can be investigated.

DISCUSSION.

(1) *Characteristics of the Oxidation of Acetaldehyde.*—In accordance with the results of other workers (cf. McDowell and Thomas, *J.*, 1949, 2208, for recent references) curves *A* and *B* of Fig. 3 confirm that the oxidation of acetaldehyde proceeds at markedly lower temperatures and more rapidly for a fuel–air mixture of 2·8 : 1 than of 1 : 1. The yields of acid and peroxide (calculated as acetic and peracetic acids) correspond with about 20% of the aldehyde actually consumed in passage through the reaction tube. Gas analysis (cf. Table II) shows the presence of some carbon monoxide and dioxide, as well as giving information on the amount of oxygen consumed. Although the oxygen is all accounted for, it is not clear what happens to the unrecovered acetaldehyde. Some of it polymerises to a rubber-like polymer which can be depolymerised on storage or boiling with water.

(2) *Effect of Hydrocarbons on the Oxidation of Acetaldehyde.*—From Fig. 4 and Table I, it is evident that the added hydrocarbon XH inhibits the oxidation of acetaldehyde, when XH is hydrogen, hexene, or heptane.

The order of increasing collision diameters (Table III) does not suggest any explanation of this inhibition in terms of a simple dilution effect.

TABLE III.

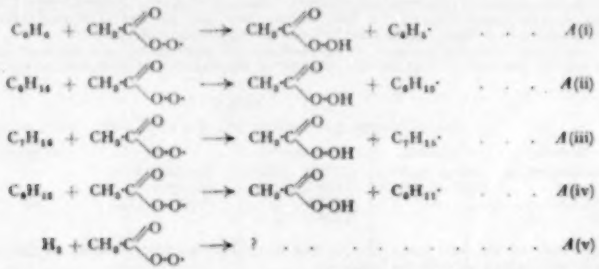
Molecule	C_6H_{14}.	N_2.	H_2.	C_6H_{14}.	C_7H_{16}.
Collision diameter, A.	4·66	3·18	2·40	5·18	5·8

Cf. Schuil, *Phil. Mag.*, 1939, **28**, 683.

When inhibition is observed it could in principle arise either by energy degradation on collision between the inhibitor and the activated chain carriers, or by chemical reaction between the inhibitor and the chain carrier. The possibility of energy degradation is discussed under

(3), but in the authors' opinion the inhibition can most readily be interpreted on the theory that acetyl peroxide radicals have a finite probability of removing hydrogen from each of the molecules XH, but with varying effectiveness. An order of increasing ease of removal would be as in *A*(i) to *A*(v) below.

From Fig. 4 it appears that the molecules nitrogen, benzene, and hexane behave substantially in the same way and may be presumed to be inert on collision with acetyl peroxide radicals. However the fact that heptane and hexene both have marked inhibitory effects could be reconciled with the apparent inertness of hexane and benzene if the probability of removal of hydrogen in the reactions *A*(i) and *A*(ii) is markedly less than that in *A*(iii) and *A*(iv). Comparatively small differences in activation energy would suffice to give this effect. For example, if the activation for *A*(ii) were 6 kcals. greater than for *A*(iii), and the temperature-independent terms in the velocity equation were the same, the rate of *A*(ii) would be one-thousandth of the rate of *A*(iii) at 460° K.



The hypothesis is that, when the reactions occur, the oxidation is inhibited because the new radicals produced fail to prolong the chains. As the temperature is raised oxidation proceeds once more, so that the inhibition is compensated. In principle this could happen either by further oxidation of aldehyde or by more important contributions to the overall oxidation from (1) and (2). So far as it has been possible to examine the condensates it seems unlikely that extensive chain oxidation of any of the hydrocarbons occurs, even at the critical reaction temperatures listed in Table I. The inference is that even when alkyl radicals are produced by reaction (*A*) it requires a higher temperature before chain oxidation of the hydrocarbon will occur at all freely. Thus *either* step (1) *or* step (2) must have an activation energy which requires the temperature of 250° before a pure paraffin will be oxidised at all freely.

What actually happens to the hydrocarbon radicals in the present set-up is still under investigation, but clearly they do not start the long oxidation chains which apply at 250° or above. It is significant that *A*(iv) occurs much more readily than *A*(ii), presumably owing to the smaller activation required to remove hydrogen atoms from the α-position relative to a double bond in an olefin, compared with the activation to remove hydrogen atoms from a paraffin (cf. Farmer, *Trans. Faraday Soc.*, 1942, **38**, 348).

(3) *Inhibition of Acetaldehyde Oxidation by Molecular Hydrogen.*—This striking effect may be akin to the inhibition of oxidation of pentane by molecular hydrogen in the region 260—280° (Prettre, *Compt. rend.*, 1936, **203**, 619. Jost (" Explosion and Combustion Processes in Gases," McGraw-Hill, 1946) has attributed this effect of hydrogen to its catalytic influence on the reaction walls. An alternative explanation may well be that energy chain transfers are important in these oxidations (Ubbelohde, *Proc. Roy. Soc.*, 1935, *A*, **152**, 369). The well known effect of hydrogen in degrading the vibrational energy by collision with carbon dioxide molecules (cf. the review in *Reports Progr. Physics*, 1948, **12**, 264) may be paralleled by its effect in degrading the vibrational energy of chain carriers before these have time to continue the succeeding links in the chain.

A third possible explanation would be that the acyl peroxide radicals use up both hydrogen atoms on collision, so that the chain is not propagated in the usual way.

QUEENS UNIVERSITY, BELFAST. [*Received, November 10th*, 1949.]

148. *Acenaphthene Series. Part III. Orientation of* tert.*-Butyl- and Di-*tert.*-butyl-acenaphthene, and Preparation of New Derivatives.*

By H. E. Nörsten and A. T. Peters.

The butylation of acenaphthene by means of *tert.*-butyl chloride and aluminium chloride, in carbon disulphide as a solvent, is shown to yield 2-*tert.*-butylacenaphthene and 2 : 5-di-*tert.*-butylacenaphthene.* The orientation of these hydrocarbons is based mainly on their oxidation to benzene-1 : 2 : 3 : 5-tetracarboxylic acid and provides the first instance of direct substitution of the acenaphthene nucleus in the 2-position.

The alkylacenaphthenes are degraded to the corresponding alkylnaphthalenes and thus a hydrocarbon, first described in 1884, has been identified as 2 : 7-di-*tert.*-butylnaphthalene.

New derivatives of 2-*tert.*-butyl- and of 2 : 5-di-*tert.*-butyl-acenaphthene are prepared.

The butylation of acenaphthene was first recorded in Part I of this series (Peters, *J.*, 1942, 562), where the reaction between a solution of the hydrocarbon in carbon disulphide and *tert.*-butyl chloride, in presence of aluminium chloride, was described. The separation of *tert.*-butylacenaphthene from the parent hydrocarbon and from the disubstituted product was a tedious process, but eventually the monoalkylacenaphthene was obtained in a small yield, but very pure, having m. p. 88—88·5°, whereas m. p. 73—74° had been recorded previously. Buu-Hoï and Cagniant (*Rev. sci.*, 1943, **81**, 72) gave m. p. 72° for *tert.*-butylacenaphthene, which they obtained in very poor yield from the products of a similar reaction without the use of a solvent.

Orientation of tert.*-Butylacenaphthene.*—Those substitution reactions of acenaphthene which lead to products that have been orientated (35 studies) are summarised in the table.

Acenaphthene is generally attacked in the 3-position, rarely in the 1-position, never in the 2-position, and in the 7-position only by oxidising agents. Some 2-substitution had been postulated but not proved in the case of benzylation.

From consideration of these results, the butylation of the hydrocarbon was expected to yield 3-*tert.*-butylacenaphthene, which orientation was accepted in Part I and by Buu-Hoï and Cagniant.

In the present research, the *tert.*-butylacenaphthene was converted into *tert.*-butylnaphthalic anhydride and this was decarboxylated to 2-*tert.*-butylnaphthalene either by distillation with soda-lime at ordinary or reduced pressure, or by mercuration and decomposition, followed by treatment with copper-bronze in boiling quinoline. The 2-*tert.*-butylnaphthalene was shown to be identical with that synthesised unambiguously by Bromby, Peters, and Rowe (*J.*, 1943, 144). This result indicated that the starting material had been 2(or 1)-*tert.*-butylacenaphthene. However, Tsukervanik and Terentieva (*J. Gen. Chem. Russ.*, 1937, **7**, 637) stated that 1-alkylnaphthalenes isomerise on heating to 2-alkylnaphthalenes and their statement received some support from Mayer and Schiffner (*Ber.*, 1934, **67**, 67) and from Cullinane and Chard (*Nature*, 1948, **161**, 690), although these workers employed temperatures above 400° and catalysts. The reaction might therefore be explained by 3-*tert.*-butylacenaphthene yielding 1-*tert.*-butylnaphthalene, which subsequently isomerised. No support could be found for this course of the degradation, for even when carried out under reduced pressure the reaction gave 2-*tert.*-butylnaphthalene only.

In spite of the negative results previously recorded, it was again attempted to oxidise *tert.*-butylnaphthalic anhydride, and benzene-1 : 2 : 3 : 5-tetracarboxylic acid was obtained by means of nitric acid under pressure. It was thus proved conclusively that the butylation of acenaphthene had yielded 2-*tert.*-butylacenaphthene. No rearrangement had therefore occurred in the degradation of this hydrocarbon to 2-*tert.*-butylnaphthalene.

The butylation of acenaphthene therefore presents the first example of direct 2-substitution therein. The abnormal orientation of the product is in agreement with the abnormal orientation frequently observed in the products of Friedel–Crafts alkylations in the benzene series (*e.g.*, Ador and Rilliet, *Ber.*, 1878, **11**, 1627; Kelbe, *Annalen*, 1881, **210**, 1; Pajeau, *Bull. Soc. chim.*, 1945, **12**, 637; Esaner and Gossin, *ibid.*, 1884, **42**, 213; Fournier, *ibid.*, 1892, **7**, 651; Heise and Töhl, *Annalen*, 1892, **270**, 155). Moreover, naphthalene is generally attacked in

* Richter's numbering of the acenaphthene system is used in this paper. The orientation of many of these compounds amends that in Parts I and II.

the β-position in Friedel–Crafts alkylations (*e.g.*, Roux, *Bull. Soc. chim.*, 1884, **41**, 379; *Ann. Chim. Phys.*, 1887, **12**, 289).

Reagent.	Position of substitution.
HNO_3 + AcOH	3 [1, 2]
Ph·CO·NO_2 or NO(OH)$(OAc)_2$	1, 3 (*ca.* 0·03% in 2) [2]
Cl_2	3 [3–7]
SO_2Cl_2	3 [7]
Br_2	3 [1, 8]
I_2 and HgO	3 [1, 8]
H_2SO_4 or Cl·SO_3H at 0°	3 [8, 9]
H_2SO_4 at 160°	1 [9]
AcCl + $AlCl_3$	3, 1 (little) [1, 10]
HOAc + HF	1 (up to 84%), 3 [10, 11]
CH_2Cl·COCl + $AlCl_3$	3, 1 [12, 13]
CH_2Br·COBr + $AlCl_3$	3 [14]
$CH_2(CN)$·COCl + $AlCl_3$	3 [15]
Et·COCl + $AlCl_3$	3, 1 (?) [16, 14]
CH_2·CH:CH·COCl + $AlCl_3$	3 [10]
CH_2·CO·O·CO·CH_2 + $AlCl_3$	3 (78%), 1 (15%) [17]
CH_2·CO·O·CO·CH_2 + HF	1, 3 [10]

Reagent.	Position of substitution.
Maleic anhydride + $AlCl_3$	3 [17]
Ph·COCl + $AlCl_3$	3 [1]
CH_2Ph·COCl + $AlCl_3$	3 [10, 18]
CH_2Ph·CO_2H + HF	3, 1 [10]
$C_6H_4(CO)_2O$ + $AlCl_3$	3 [1, 10]
NH_2·COCl + $AlCl_3$	3 [21, 18]
$(COCl)_2$	3 [22]
Phenylethyluronium chloride + $AlCl_3$	3 [23]
CNBr + $AlCl_3$	3 [24, 25]
CH_2O + P_2O_5	3 [26]
$COCl_2$ + $AlCl_3$	3 [25]
HCN or H·C(NH)·NHCHCl + $AlCl_3$	2 [27, 28]
H·CONMePh + $POCl_3$	3 [29]
EtBr + $AlCl_3$	3(?) [30]
CH_2PhCl + $ZnCl_2$, etc.	3, 2(?) [29–33]
PbO_2 + HOAc	7 [33]
$Pb(OAc)_4$ + HOAc at 60—70°	7 [34–37]
Cl_2 or Br_2 in sunlight	7 [38]

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1-*tert.*-Butylacenaphthene, a liquid, b. p. 155—160°/0·8 mm., was synthesised by Buu-Hoi and Cagniant (*Rev. sci.*, 1942, **80**, 176) and was therefore quite different from the hydrocarbon under discussion.

*Orientation of Di-*tert.*-butylacenaphthene.*—By analogy with the other reactions of acenaphthene and of monosubstituted acenaphthenes, it had been assumed that the di-*tert.*-butylacenaphthene formed in the butylation of acenaphthene had the 3 : 4-structure. However, di-*tert.*-butylacenaphthene was easily oxidised by sodium dichromate in boiling acetic acid to di-*tert.*-butylnaphthalic anhydride, which by means of nitric acid under pressure was converted into benzene-1 : 2 : 3 : 5-tetracarboxylic acid. Here, as in the case of the *tert.*-butylnaphthalic anhydride, relatively high concentrations of nitric acid could be used in the oxidation, as the carbonyl groups deactivated the nucleus sufficiently to prevent nitration. The formation of benzene-1 : 2 : 3 : 5-tetracarboxylic acid proved that at least one *tert.*-butyl group of di-*tert.*-butylacenaphthene is *meta* to the acenaphthene bridge and that one such group is in each ring of the naphthalene nucleus.

Mercuration and decomposition of di-*tert.*-butylnaphthalic acid produced only one *di-tert.-butylnaphthoic acid*, whereas mercuration and decomposition of *tert.*-butylnaphthalic acid had produced a difficultly separable mixture of two tert.-*butylnaphthoic acids*. It was concluded that the di-*tert.*-butylacenaphthene molecule must be symmetrical, and must consequently be 2 : 5-di-*tert.*-butylacenaphthene.

This structure explained the observed *ace*-substitution in the dinitration and the postulated

ace-substitution in dichlorination and dibromination of the hydrocarbon (see below and in Part II, Peters, *J.*, 1947, 742). The first substituent would enter the 3-position, but as the 4-position is blocked by such bulky groups in the 2-, 3-, and 5-positions, the second substituent would be forced to attack the acenaphthene bridge. *ace*-Substitution cannot be explained by the previously accepted 3 : 4-structure.

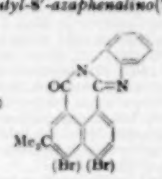
Derivatives of 2-tert.-*Butylacenaphthene and* 2 : 5-*Di*-tert.-*butylacenaphthene.*—Several new derivatives of 2-*tert.*-butylacenaphthene were prepared. From the facts that two *mononitro*-2-tert.-*butylacenaphthenes* were isolated and that *bromo*-2-tert.-*butylacenaphthene* was only obtained in an impure condition even after repeated crystallisation, it can be deduced that in the 2-*tert.*-butylacenaphthene molecule two positions are approximately equally reactive. These are probably the 3 : 4-positions. If, as was done in the case of bromination, the reaction is carried to the di-substituted stage, one product only is obtained in a satisfactory yield and almost immediately in a pure state.

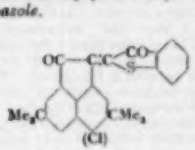
The reaction of *dibromo*-3-tert.-*butylnaphthalic anhydride* with methylamine was of interest, for not only was the compound converted into its *N*-methylimide, but, also, even under mild conditions, one of the bromine atoms was replaced by a methylamino-group. Under similar conditions, ammonia only gave the *imide* and left the bromine atoms unaffected. *o*-Phenylenediamine yielded the yellow *dibromo*-9′-*keto*-2′(or 5′)-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 1)-*benziminazole* (I).

From the general rules of substitution and from those of acenaphthene substitution, it can be assumed that the 3-position of 2 : 5-di-*tert.*-butylacenaphthene is the most reactive. The nomenclature of the many derivatives recorded in Part II must therefore be amended accordingly, the *tert.*-butyl groups being at positions 2 and 5, and the nitro- or bromo-group at 3.

Some further derivatives have now been prepared. Although 2 : 5-di-*tert.*-butylacenaphthene would not react with chlorine in chloroform solution, reaction proceeded smoothly in carbon tetrachloride. 3-*Chloro*-2 : 5-*di*-tert.-*butylacenaphthene* was also prepared, but less satisfactorily, by means of sulphuryl chloride in chloroform solution. The chloro-compound was oxidised, and in addition to the naphthalic anhydride derivative, some quinone was formed, as shown by its ability to condense with 3-hydroxythionaphthen to give the red 3′(or 4′)-*chloro*-2′ : 5′-*di*-tert.-*butyl*-2 : 7′-*thionaphthenacenaphthenylindigo* (II). The 4-*chloro*-3 : 6-*di*-tert.-*butylnaphthalic anhydride* yielded *imides* and also the canary-yellow 3′(or 4′)-*chloro*-9′-*keto*-2′ : 5′-*di*-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′-2 : 1)*benziminazole.*

(I.)





(II.)

The hydrocarbon reacted with 2 mols. of chlorine to give a *dichloro*-2 : 5-*di*-tert.-*butylacenaphthene.* As this compound lost much of its chlorine content upon oxidation, it can be assumed that the second chlorine atom had entered one of the *ace*-positions (cf. dinitro-2 : 5-di-*tert.*-butylacenaphthene; Part II).

2 : 7-*Di*-tert.-*butylnaphthalene.*—Two di-*tert.*-butylnaphthalenes have often been isolated; Gump (*J. Amer. Chem. Soc.*, 1931, **53**, 380) first recognised them as such, but Wegscheider (*Monatsh.*, 1884, **5**, 236) was the first to prepare them. One, m. p. 146—147°, will not form a picrate; the other (recorded m. p.s varying between 80° and 95°) gives a picrate, m. p 157—158°. Tsukervanik and Terentieva (*loc. cit.*) are alone in recording m. p. 132°, picrate, m. p. 99°, for a di-*tert.*-butylnaphthalene.

Contractor, Peters, and Rowe (*J.*, 1949, 1993) obtained the above two hydrocarbons by the action of *tert.*-butyl chloride and aluminium chloride on 2-*tert.*-butylnaphthalene, which had been orientated by Bromby *et al.* (*loc. cit.*), thus showing that one *tert.*-butyl group in each of these hydrocarbons must be in a β-position. They also oxidised the lower-melting isomer by means of potassium permanganate to an acid, the composition of which corresponded to that of a mono-*tert.*-butylphthalonic acid. They therefore concluded that the lower-melting isomer contained the *tert.*-butyl groups in different rings.

Price, Shafer, Huber, and Bernstein (*J. Org. Chem.*, 1942, **7**, 517) decomposed the picrate, m. p. 156—156·5°, to obtain a hydrocarbon, m. p. 80—82°, raised by repeated recrystallisation

to 103—104°. A mixture consisting of 2 parts of this recrystallised product, m. p. 103—104°, and 1 part of the di-*tert.*-butylnaphthalene, m. p. 145—146°, melted at 80—82° and was identical with the hydrocarbon, m. p. 80—82°, obtained by decomposition of the picrate, m. p. 156—156·5°. The picrate was thus composed of 2 mols. of di-*tert.*-butylnaphthalene, m. p. 103—104°, 1 mol. of di-*tert.*-butylnaphthalene, m. p. 145—146°, and 2 mols. of picric acid, which constitution was supported by the analyses obtained.

In the present research, a specimen of the picrate, m. p. 157—158°, was analysed, and its constitution agreed with that given by the above authors. It was decomposed, and the hydrocarbon obtained was repeatedly crystallised from alcohol to give colourless, silky needles, m. p. 102—103°. These needles were converted into a *picrate*, an egg-yolk-coloured powder, m. p. 145—146°, not previously prepared. This picrate was dissolved in dry alcohol and the required amount of the di-*tert.*-butylnaphthalene, m. p. 145—146°, dissolved in the same solvent, was added. The mixture was boiled and, on cooling, the orange needles of the picrate, m. p. 157—158°, separated. They gave analyses agreeing with the formula given by Price *et al.* and they showed no depression of m. p. on admixture of the starting material.

Decarboxylation of **3**:6-di-*tert.*-butylnaphthalic anhydride by soda–lime distillation, by copper-bronze in boiling quinoline, or by mercuration and decomposition, followed by copper-bronze in boiling quinoline, yielded the di-*tert.*-butylnaphthalene, m. p. 102·5—103·5° (picrate, m. p. 145—145·5°). This hydrocarbon is therefore **2**:7-*di*-tert.-*butylnaphthalene*, which formula satisfies the requirements laid down by Contractor *et al.*

The research is being extended to show whether other Friedel-Crafts alkylations of acenaphthene yield 2-substituted derivatives, whether alkylating agents other than alkyl halide and aluminium chloride yield differently orientated products, and what action aluminium chloride has on alkylacenaphthenes.

Experimental.

(M.p.s are corrected. Micro-analyses were carried out by Drs. Weiler and Strauss, Oxford.)

2-tert.-*Butylacenaphthene*.—A mixture of acenaphthene (308 g., 1 mol.), carbon disulphide (750 c.c.), and aluminium chloride (54 g., 0·2 mol.) was stirred at room temperature and *tert.*-butyl chloride (218 c.c., 1 mol.) was added dropwise during one hour. Stirring was continued at room temperature for 3 hours, and the whole then heated under reflux for 2 hours. After standing overnight, the carbon disulphide solution was poured off and there remained a mixture of granular and tarry complex, which consisted mainly of di-*tert.*-butylacenaphthene and aluminium chloride. The carbon disulphide solution was filtered through charcoal, solvent removed, and the residue distilled at 765 mm. (269 g., 64%). The fractions, b. p. 290—335°, were redistilled at 7 mm., and the part, b. p. 160—174° (66 g., 16%), collected. This was recrystallised twice from acetic acid and then from methyl alcohol, giving colourless plates, m. p. 88—88·5° (Found: C, 91·35; H, 8·6. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%) (Part I: m. p. 73—74° for supposed 3-isomer). The distillation under reduced pressure proved difficult but was indispensable, because fractional distillation at ordinary pressure and fractional crystallisation from a variety of solvents (ethyl alcohol, methyl alcohol, 2-ethoxyethanol, and acetic acid) failed to separate the *tert.*-butylacenaphthene from acenaphthene and di-*tert.*-butylacenaphthene. The difficulty was that the distillates solidified very readily and that the substances involved sublimed easily; the apparatus therefore often became obstructed, yet any rise in pressure caused by such a blockage upset the separation, which can only be controlled by the temperature of distillation.

The above experiment was the best of the many carried out under various conditions. Nitrobenzene, used instead of carbon disulphide, proved unsuccessful as a solvent. On redistillation, the *tert.*-butylacenaphthene distilled at 130—140°/1 mm.

The *picrate* separated in clusters of orange, microcrystalline needles, m. p. 121—123° (Found: C, 60·4; H, 4·8; N, 10·0. $C_{14}H_{16}C_6H_3O_7N_3$ requires C, 60·1; H, 4·8; N, 9·6%). A styphnate could not be prepared.

The **1**:**3**:5-*trinitrobenzene* complex was obtained as a yellow, microcrystalline powder, m. p. 149—150°, softening at 145° (Found: N, 10·3. $C_{16}H_{16}C_6H_3O_6N_3$ requires N, 9·9%).

Reaction between **3**-*Bromoacenaphthene and* tert.-*Butyl Chloride*, tert.-*Butyl Bromide*, *or* n-*Butyl Bromide in Presence of Sodium*.—To a solution of 3-bromoacenaphthene (10 g.) and *tert.*-butyl chloride (6 c.c., 1·25 mols.) in sodium-dried ether (50 c.c.) was added finely-divided sodium (1·5 g., 1·5 mols.), and the whole was heated under reflux for 3 hours. From the products, only 3-bromoacenaphthene could be isolated. A similar experiment with *tert.*-butyl bromide also afforded only unchanged bromoacenaphthene.

n-Butyl bromide and 3-bromoacenaphthene reacted spontaneously under conditions similar to the above, and after 2 hours' refluxing only acenaphthene, m. p. and mixed m. p. 93—94°, was isolated (cf. reaction between 3-bromoacenaphthene and n-butylmagnesium bromide; Kharasch, Sayles, and Fields, *J. Amer. Chem. Soc.*, 1944, **66**, 481).

3-tert.-*Butylnaphthalic Anhydride*.—This was prepared by oxidation of 2-*tert.*-butylacenaphthene essentially as described in Part I, but on about a double scale; it had m. p. 203—204° (yield 56%), raised by recrystallisation from acetic acid to 204—205°, depressed to below 180° on admixture with **3**:6-di-*tert.*-butylnaphthalic anhydride, m. p. 211—212°. In Part II, m. p. 201—202° was recorded for the supposed 4-isomer.

N-(2-*Hydroxyethyl*)-3-tert.-*butylnaphthalimide*.—To a solution of 3-*tert.*-butylnaphthalic anhydride in boiling alcohol was added an excess of aqueous ethanolamine. The solution was kept at the boil for

15 minutes and then allowed to cool. Colourless, silky needles separated and were recrystallised from absolute alcohol; m. p. 167—168° (Found: C, 72·7; H, 6·4; N, 4·6. $C_{14}H_{11}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%).

Oxidation of 3-tert.-*Butylnaphthalic anhydride.*—(*a*) *With potassium permanganate.* Potassium permanganate (10 g.) was added to a solution of 3-*tert.*-butylnaphthalic anhydride (2 g.) in boiling 2·5% aqueous sodium hydroxide (100 c.c.), and the whole left on a steam-bath for 3 days; it was then almost decolorised. A little alcohol was added to destroy any excess of permanganate and the manganese dioxide was filtered off. The filtrate was acidified and extracted with ether. The ether was removed from the extract and the residue was stirred with ligroin; a solid separated which was extracted with ligroin–chloroform and left a white powder, m. p. 207—208° (decomp.; shrinking from 200°) (Found: C, 56·0; H, 4·6. $C_{14}H_{14}O_7$ requires C, 57·15; H, 4·8%). It was impossible to crystallise this acid. Its *trimethyl* ester, prepared by means of diazomethane, after repeated crystallisation from aqueous methyl alcohol, formed beautiful, colourless needles, m. p. 127—129° (Found: C, 60·45, 60·6; H, 6·1, 5·8. $C_{17}H_{20}O_7$ requires C, 60·7; H, 6·0%). The acid is therefore probably 4-tert.-*butyl*-2:6-*dicarboxybenzoylformic acid* [cf. Graebe and Bossel, *Annalen*, 1896, **290**, 206; Randall, Benger, and Groocock, *Proc. Roy. Soc.*, 1938, *A*, **165**, 432, who obtained 2:6-dicarboxybenzoylformic acid by alkaline permanganate oxidation of naphthalic anhydride and of acenaphthene, acenaphthenequinone, and 3-(*o*-carboxybenzoyl)acenaphthene, respectively].

(*b*) *With nitric acid.* 3-*tert.*-Butylnaphthalic anhydride (0·5 g.), concentrated nitric acid (3 c.c.), and water (2 c.c.) were heated in a sealed tube to 200—220° for 24 hours. The solution was evaporated until solid began to separate and then allowed to cool. The solid was collected, and dried at 100° and then *in vacuo* over phosphoric oxide and sodium hydroxide, to give a white powder, m. p. 240—255° (decomp.), and at 240° as the anhydride (Found: C, 46·3, 46·2; H, 2·2, 2·3. Calc. for $C_{16}H_4O_8$: C, 47·25; H, 2·4%). An aqueous solution of the acid gave, on standing, a white precipitate with barium chloride solution, a reaction not given by benzene-1:2:3:4-tetracarboxylic acid.

The acid (0·25 g.) was covered with ether (10 c.c.), and diazomethane solution (from nitrosomethylurethane, 3 c.c.) was added. Vigorous frothing occurred and after 30 minutes the solid was filtered off; it was an almost colourless nitrogen-containing powder, which shrank a little below 300°, but on further heating it turned yellow and eventually gave off a gas and charred with a little explosion. The filtrate was evaporated to dryness, and the solid crystallised three times from methyl alcohol to give colourless needles, m. p. 106—107°, depressed to 90—93° on admixture of tetramethyl benzene-1:2:3:4-tetracarboxylate (Found: C, 52·9, 53·0; H, 4·5, 4·3. Calc. for $C_{14}H_{14}O_8$: C, 54·2; H, 4·5%).

The product of oxidation with nitric acid was therefore mainly benzene-1:2:3:5-tetracarboxylic acid (cf. Bamford and Simonsen, *J.*, 1910, **97**, 1904; Smith and Byrkit, *J. Amer. Chem. Soc.*, 1933, **55**, 4395). The impurities are probably due to products arising from attack on the nucleus carrying the *tert.*-butyl group.

tert.-*Butyl*-1-*naphthoic Acids* (cf. method of mercuration: Leuck, Perkins, and Whitmore, *J. Amer. Chem. Soc.*, 1929, **51**, 1835; Davies, Heilbron, and Irving, *J.*, 1932, 2715).—Finely-ground 3-*tert.*-butylnaphthalic anhydride (10 g.) was dissolved in water (500 c.c.) containing sodium hydroxide (6·3 g., 4 mols.) by refluxing for some time, a large flask (2 l.) being used in order to avoid frothing over in the later stage. A boiling solution of mercuric oxide (8·6 g., 1 mol.) in a mixture of acetic acid (13 c.c.) and water (37 c.c.) was added, and the slightly red mixture, which was acid to litmus, was refluxed for 98 hours, during which the precipitate became a pure white. It was filtered off, washed, and refluxed with concentrated hydrochloric acid (100 c.c.) and water (200 c.c.) for 2 hours. A lump of solid was formed and this was dissolved in much alcohol. The solution was filtered from a finely-divided white solid, which was insoluble in sodium hydroxide solution and did not melt below 300°. The alcoholic solution was filtered (charcoal) and evaporated to approximately 50 c.c. It was allowed to cool and the precipitate collected. The tert.-*butyl*-1-*naphthoic acid* (1·5 g.) crystallised from alcohol in colourless, irregular crystals, m. p. 167—169° (with previous sintering), unaltered by recrystallisation (Found: C, 79·4; H, 7·2. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·0%).

The residues were evaporated to dryness, yielding a cream-coloured powder, m. p. 110—150° (4·4 g.), which had a distinct odour of 2-*tert.*-butylnaphthalene. Fractional crystallisation from aqueous methyl alcohol, with rejection of the least soluble portions, gave some colourless plates and rods, m. p. 124—127°, of an isomeric tert.-*butyl*-1-*naphthoic acid* (Found: C, 78·9; H, 7·1%).

2-tert.-*Butylnaphthalene.*—(*a*) *From* tert.-*butylnaphthalic anhydride.* 3-*tert.*-Butylnaphthalic anhydride (5 g.) was distilled with soda-lime, giving a small yield of a colourless oil, b. p. 270° (uncorr.), which was converted into a picrate, m. p. 98—99°, not depressed on admixture of authentic 2-*tert.*-butylnaphthalene picrate (Found: C, 57·65; H, 4·7; N, 10·0. Calc. for $C_{14}H_{16}C_6H_3O_7N_3$: C, 58·1; H, 4·6; N, 10·2%). When the experiment was repeated under reduced pressure (*ca.* 20 mm.), a mixture of unchanged anhydride and an oil was obtained. The latter, b. p. 275°, gave 2-*tert.*-butylnaphthalene picrate, m. p. and mixed m. p. 98—99°.

(*b*) *From the* tert.-*butyl*-1-*naphthoic acids.* The crude acids (7 g.) (see above) were boiled with quinoline (20 c.c.) and copper-bronze (2·5 g.) (Sheppard, Winslow, and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2083) and the mixture was distilled with steam after acidification with hydrochloric acid. Ether extraction of the distillate and evaporation of the ether gave a colourless oil (2 g., 39%). The picrate, m. p. 99—100°, prepared from it, showed no depression of m. p. on admixture with authentic 2-*tert.*-butylnaphthalene picrate (Found: C, 58·2; H, 4·6; N, 10·2%).

Bromo-2-tert.-*butylacenaphthene.*—To a solution of 2-*tert.*-butylacenaphthene (3 g.) in cold carbon tetrachloride (50 c.c.) was added slowly and with shaking a solution of bromine (1·3 c.c., 1·1 mols.) in the same solvent (50 c.c.). The mixture was kept with occasional shaking for 1 hour, much hydrogen bromide being evolved. The carbon tetrachloride was gradually replaced by absolute alcohol, and the solution allowed to cool. Tars were obtained and these were crystallised to give three fractions, each of which gave, on repeated crystallisation from alcohol, colourless needles, m. p. 145° (Found: C, 68·2; H, 6·75; Br, 26·05. $C_{16}H_{17}Br$ requires C, 66·4; H, 5·9; Br, 27·7%). The *bromo*-2-tert.-*butylacenaphthene* obtained was therefore impure.

Dibromo-2-tert.-butylacenaphthene.—Bromine (1·9 c.c., 2 mols.), dissolved in chloroform (40 c.c.), was added slowly and with shaking to a solution of 2-*tert.*-butylacenaphthene (4 g.) in the same solvent (50 c.c.). The mixture was kept with occasional shaking for 3 hours and then a portion of the chloroform was replaced by absolute alcohol. On cooling, *dibromo-2-tert.-butylacenaphthene* (4·2 g., 60%) was deposited and recrystallised from absolute alcohol–chloroform in colourless pillars, m. p. 185—185·5° (Found: C, 52·6; H, 4·5; Br, 43·5. $C_{16}H_{16}Br_2$ requires C, 52·2; H, 4·35; Br, 43·5%). It did not form a picrate in alcoholic solution.

Dibromo-3-tert.-butylnaphthalic Anhydride.—To a solution of dibromo-2-*tert.*-butylacenaphthene (2 g.) in boiling acetic acid (100 c.c.), sodium dichromate (8 g.) was added gradually and the solution was heated under reflux for 4 hours, then poured into water; after standing, the colourless precipitate was filtered off and extracted with boiling 5% aqueous sodium carbonate. The extract was acidified, and the resulting solid crystallised from acetic acid containing a little acetic anhydride in colourless, silky needles and plates, m. p. 218—219° (Found: C, 46·95; H, 2·9; Br, 39·5. $C_{16}H_{10}O_3Br_2$ requires C, 46·6; H, 2·9; Br, 38·8%), both forms separating simultaneously; this phenomenon was also noticed with 3 : 6-di-*tert.*-butylnaphthalic anhydride.

Derivatives of Dibromo-3-tert.-butylnaphthalic Anhydride.—On being heated under reflux with excess of aqueous ammonia (*d* 0·88), an alcoholic solution of the anhydride gave *dibromo-3-tert.-butylnaphthalimide*, which crystallised from absolute alcohol in very pale yellow plates, m. p. 294—295° (Found: N, 3·4; Br, 38·3. $C_{16}H_{13}O_2NBr_2$ requires N, 3·4; Br, 38·9%). On using 33% aqueous methylamine instead of ammonia in a similar reaction, there were obtained lemon-coloured needles, m. p. 301—302° (Found: N, 6·35; Br, 22·2. $C_{17}H_{15}O_2N_2Br$ requires N, 7·5; Br, 21·3%. $C_{17}H_{15}O_2NBr_2$ requires N, 3·3; Br, 37·6%). In the reaction with methylamine, therefore, not only was the *N*-methylimide formed, but one bromine atom had been replaced to a large extent by a methylamino-group. The anhydride (0·5 g.) and *o*-phenylenediamine (0·15 g.), refluxed in acetic acid for 15 minutes, afforded *dibromo-9'-keto-2'(or 5')-tert.-butyl-8'-anaphenalino(7' : 8'-2 : 1)benziminazole*, which crystallised from acetic acid in yellow needles, m. p. 250—251° (Found: N, 5·7; Br, 33·4. $C_{23}H_{16}ON_2Br_2$ requires N, 5·8; Br, 33·1%).

Nitro-2-tert.-butylacenaphthenes.—To a cold solution of 2-*tert.*-butylacenaphthene (5 g.) in acetic acid (200 c.c.) was added nitric acid (1·65 c.c., 1·1 mols.) dissolved in acetic acid (50 c.c.); the solution, which turned yellow, was kept for 1 hour, then evaporated to small bulk. On cooling, a yellow semi-crystalline precipitate separated and this was crystallised three times from absolute alcohol, yielding yellow plates, m. p. 158—159° (0·4 g.) (Found: C, 75·1; H, 6·5; N, 5·7. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%). From the mother-liquor was obtained by repeated crystallisation from alcohol a very small quantity of yellow needles, m. p. 208—210°, with previous softening (Found: N, 5·9%). Two isomeric *nitro-2-tert.-butylacenaphthenes* were therefore formed in the nitration of the hydrocarbon.

Nitro-3-tert.-butylnaphthalic Anhydride.—Oxidation of the nitro-2-*tert.*-butylacenaphthene, m. p. 158—159° (0·4 g.), with sodium dichromate (2 g.) in boiling acetic acid (30 c.c.) for 3 hours yielded, by the usual procedure, some yellow crystalline masses and plates, m. p. 194—195°, of *nitro-3-tert.-butylnaphthalic anhydride* (Found: C, 64·6; H, 4·6; N, 4·6. $C_{16}H_{11}O_5N$ requires C, 64·2; H, 4·35; N, 4·7%).

2 : 8-*Di*-tert.-*butylacenaphthene* (cf. Part I).—This was prepared essentially as described formerly for the supposed 3 : 4-isomer, but on a four-fold scale; it formed colourless needles, m. p. 162·5—163·5° (Part I, 162—163°). There remained in the flask a fluorescent, orange tar, which on cooling set to a glass, b. p. *ca.* 220°/0·8 mm. (Found: H, 9·3. Calc. for $C_{24}H_{34}$: H, 10·6%). This analysis does not support Buu-Hoï and Cagniant's suggestion (*loc. cit.*) that this consisted of tri-*tert.*-butylacenaphthene. The glass may be of the nature of the yellow-green, fluorescent oil obtained by Niggemann (*Chem. Zentr.*, 1919, II, 584) by boiling acenaphthene with aluminium chloride.

The picrate had m. p. 165—165·5° (Part I, 164°). The 1 : 3 : 5-trinitrobenzene complex was obtained in orange rosettes of needles, m. p. 205—206°, from absolute alcohol (Found: N, 8·75. Calc. for $C_{30}H_{34}C_9H_3O_6N_3$: N, 8·8%).

3 : 6-*Di*-tert.-*butylnaphthalic anhydride* (cf. Part I).—The hydrocarbon was oxidised as before to this anhydride; m. p. 211—212° (211° in Part I for supposed 4 : 5-isomer).

N-(2-*Hydroxyethyl*)-3 : 6-*di*-tert.-*butylnaphthalimide.*—To a solution of the anhydride (1 g.) in boiling alcohol (60 c.c.) was added an excess of aqueous ethanolamine and the whole was heated on the steam-bath for 10 minutes. The *naphthalimide*, which separated on cooling, crystallised from alcohol in silky, colourless needles (0·8 g.), m. p. 248° (Found: C, 75·0; H, 7·6; N, 4·4. $C_{28}H_{37}O_3N$ requires C, 74·8; H, 7·65; N, 4·0%).

Nitric Acid Oxidation of 3 : 6-*Di*-tert.-*butylnaphthalic Anhydride.*—A mixture of the anhydride (0·75 g.), water (2 c.c.), and concentrated nitric acid (4 c.c.) was heated in a sealed tube at 160—180° for 24 hours. Two such experiments yielded a few insoluble pale yellow plates, m. p. up to 170°, which were filtered off. The filtrate was evaporated to dryness, yielding a white powder, which under the microscope appeared as masses of tiny crystals. These melted at 252—254°, shrinking a little before this temperature was reached and giving an opaque liquid which decomposed at 256—257°. On cooling, the liquid solidified immediately and on reheating was clear again by 237°. The powder was extremely soluble in water and an aqueous solution gave, on standing, a white, microcrystalline precipitate with barium chloride solution. The powder was benzene-1 : 2 : 3 : 5-tetracarboxylic acid (Found: C, 47·0; H, 2·4. Calc. for $C_{10}H_6O_8$: C, 47·2; H, 2·4%). The tetramethyl ester was prepared by means of diazomethane in ethereal solution and, after crystallising twice from methyl alcohol, formed rosettes of colourless plates, m. p. 109—110° (Found: C, 53·95; H, 4·3. Calc. for $C_{14}H_{14}O_8$: C, 54·2; H, 4·5%).

In another experiment under the same conditions but with 1·0 g. of anhydride, the solution was not evaporated to dryness, but was allowed to crystallise when it had been reduced to small bulk. Rosettes of needles were obtained and these, crystallised from water, softened at 180°, and melted at 195—198° (Found: C, 54·6; H, 5·6. $C_{12}H_{14}O_6$ requires C, 58·6; H, 5·3%); when dissolved in water they gave an immediate precipitate with barium chloride solution. The analysis approximated to that

of a tert.-*butylbenzenetricarboxylic acid*. It can be concluded with certainty that the naphthalene ring had been oxidised before the butyl group was attacked.

3-*Chloro*-2 : 5-*di*-tert.-*butylacenaphthene*.—To a cold solution of 2 : 5-di-*tert*.-butylacenaphthene (10 g.) in carbon tetrachloride (50 c.c.) was slowly added with frequent shaking during 30 minutes a solution of chlorine (3 g., 1·1 mols.) in the same solvent (50 c.c.); the solution was then kept with occasional shaking for 1 hour. Most, but not all, of the carbon tetrachloride was then evaporated off, and the remainder gradually replaced by absolute alcohol. On cooling, slightly yellow needles (7·8 g., 69%), m. p. 118—119°, separated. By repeated crystallisation from absolute alcohol, 3-*chloro*-2 : 5-*di*-tert.-*butylacenaphthene* was obtained as colourless rods, m. p. 124—125° (Found : C, 80·2; H, 8·4; Cl, 12·2. $C_{20}H_{31}Cl$ requires C, 79·9; H, 8·4; Cl, 11·8%). In chloroform solution, or in hot acetic acid, there was no reaction between chlorine and the hydrocarbon.

Alternatively, sulphuryl chloride (3·1 c.c., 1 mol.) was added to a solution of 2 : 5-di-*tert*.-butylacenaphthene (10 g.) in chloroform (50 c.c.); after reaction had subsided, the mixture was heated under reflux for 2 hours, then poured into absolute alcohol, and the whole partly concentrated, then cooled. Impure 3-chloro-2 : 5-di-*tert*.-butylacenaphthene (7 g., 62%) crystallised out in yellow rods, m. p. 118—119°. This product was not as pure as that obtained above; from the most insoluble portion some orange needles, m. p. 299—300° (Found : Cl, 5·4%), were isolated.

3-*Chloro*-2 : 5-*di*-tert.-*butylacenaphthene picrate* was obtained from alcoholic solution as red needles, m. p. 151—152° (Found : N, 7·9; Cl, 7·4. $C_{26}H_{34}ClC_6H_3O_7N_3$ requires N, 7·9; Cl, 6·7%).

4-*Chloro*-3 : 6-*di*-tert.-*butylnaphthalic Anhydride*.—3-Chloro-2 : 5-di-*tert*.-butylacenaphthene (3·5 g.) was dissolved in boiling acetic acid (150 c.c.), and sodium dichromate (12 g.) added gradually. The whole was refluxed for 2 hours, poured on ice–water, and filtered off after standing. The pale yellow powder (3·3 g., 82%) thus obtained was crystallised once from acetic acid and once from absolute alcohol, yielding colourless, irregular plates of the *anhydride*, m. p. 170·5—171° (Found : C, 69·8; H, 5·8; Cl, 10·9. $C_{20}H_{21}O_3Cl$ requires C, 69·7; H, 6·1; Cl, 10·3%).

The *naphthalimide* crystallised from absolute alcohol in colourless needles, m. p. 294° (Found : C, 70·3; H, 6·6; N, 4·2; Cl, 9·7. $C_{20}H_{22}O_2NCl$ requires C, 69·9; H, 6·4; N, 4·1; Cl, 10·3%). The *N-methylimide* separated from alcoholic solution in colourless needles, m. p. 265° (Found : N, 4·2. $C_{21}H_{24}O_2NCl$ requires N, 3·9%). 2′(or 4′)-*Chloro*-9′-*keto*-2′ : 5′-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 1)-*benziminazole* crystallised from acetic acid in canary-yellow rods, m. p. 270—272° (Found : N, 7·2. $C_{28}H_{23}ON_3Cl$ requires N, 6·7%).

3′(or 4′)-*Chloro*-2′ : 5′-*di*-tert.-*butyl*-2 : 7′-*thionaphthenacenaphthenylindigo*.—To a solution of 3-chloro-2 : 5-di-*tert*.-butylacenaphthene (3 g.) in boiling acetic acid (50 c.c.) was added all at once roughly ground sodium dichromate (10 g.), and the mixture was stirred and kept gently boiling for 4 minutes after the reaction had subsided. It was poured on ice–water and filtered. The solid (3 g.) was extracted 6 times with boiling 5% aqueous sodium carbonate (1 l.). Acidification of the combined extracts yielded 4-chloro-3 : 6-di-*tert*.-butylnaphthalic anhydride (1·5 g.). The insoluble, straw-coloured residue, m. p. 135—138° (1·3 g.), was condensed with 2-hydroxythianaphthen by boiling in acetic acid–hydrochloric acid (10 : 1) for 5 minutes to yield a thioindigoid *dye*, which crystallised from acetic acid in bright red needles, m. p. 269—270° (0·4 g.) (Found : Cl, 7·5; S, 7·0. $C_{32}H_{32}O_2ClS$ requires Cl, 7·7; S, 6·95%). This was equivalent to the presence of 0·3 g. of 3-chloro-2 : 5-di-*tert*.-butylacenaphthenequinone, which was thus formed in 9% yield in the above reaction.

3 : 7(or 8)-*Dichloro*-2 : 5-*di*-tert.-*butylacenaphthene*.—2 : 5-Di-*tert*.-butylacenaphthene (5 g.) was dissolved in carbon tetrachloride (50 c.c.) and, during 30 minutes, a solution of chlorine (2·7 g., 2 mols.) in the same solvent (50 c.c.) was added with shaking. The solution was kept for another 30 minutes, and some of the carbon tetrachloride was then evaporated and the remainder gradually replaced by absolute alcohol. On cooling, there separated an oil, which on repeated crystallisation from absolute alcohol yielded colourless needles, m. p. 139—141° (0·5 g., 8%) (Found : C, 71·5; H, 6·9; Cl, 21·1. $C_{20}H_{30}Cl_2$ requires C, 71·6; H, 7·2; Cl, 21·2%).

Oxidation of the *dichloro*-compound with sodium dichromate in acetic acid solution gave a small quantity of solid, which crystallised from aqueous alcohol in small irregular plates, m. p. 170—172°, not depressed on admixture of authentic 4-chloro-3 : 6-di-*tert*.-butylnaphthalic anhydride (Found : C, 68·9; H, 5·7; Cl, 11·8. Calc. for $C_{20}H_{31}O_3Cl$: C, 69·7; H, 6·1; Cl, 10·3%). These results suggested that the second chlorine atom had entered the di-*tert*.-butylacenaphthene molecule in one of the *ace*-positions.

3 : 6-*Di*-tert.-*butyl*-1-*naphthoic Acid*.—Finely-powdered 3 : 6-di-*tert*.-butylnaphthalic anhydride (13 g.) was boiled with a solution of sodium hydroxide (10 g.) in water (500 c.c.) but only partly dissolved. A hot solution of mercuric oxide (9·1 g.) in a mixture of acetic acid (10 c.c.) and water (30 c.c.) was added. A reddish precipitate formed and the whole was heated under reflux for 80 hours in a 2-l. flask. The precipitate gradually became white; it was filtered off; some globules of mercury had formed. The solid was boiled with dilute hydrochloric acid for 2 hours and filtered off. The insoluble material was dissolved in acetic acid, and the solution filtered from a white substance, m. p. >300°, and allowed to cool. 3 : 6-*Di*-tert.-*butyl*-1-*naphthoic acid* (5 g., 42%) separated, and two recrystallisations from acetic acid, in which it is very soluble, gave small clusters of crystals, m. p. 197—198° (Found : C, 80·3; H, 8·4. $C_{19}H_{28}O_2$ requires C, 80·3; H, 8·45%). A second crop (3·7 g., 31%) was obtained and from it crude di-*tert*.-butylnaphthoic acid and crude di-*tert*.-butylnaphthalic anhydride could be isolated.

Derivatives of 3 : 6-*di*-tert.-*butyl*-1-*naphthoic acid*. From absolute alcohol, the *amide* was obtained as colourless, microcrystalline needles, m. p. 212—213° (Found : N, 5·05. $C_{19}H_{29}ON$ requires N, 4·95%), and the p-*toluidide* as colourless, irregular plates, m. p. 221·5—222·5° (Found : N, 3·35. $C_{26}H_{33}ON$ requires N, 3·75%).

2 : 7-*Di*-tert.-*butylnaphthalene*.—*From* 3 : 6-*di*-tert.-*butylnaphthalic anhydride*. Soda-lime distillation of 3 : 6-di-*tert*.-butylnaphthalic anhydride (5 g.) yielded, on crystallisation from aqueous alcohol, colourless needles, m. p. 102—103° (0·5 g.). Refluxing the anhydride (5 g.) with quinoline (10 c.c.) and copper-bronze (2·5 g.) for 50 minutes and steam-distilling the product from an acid solution gave a substance, m. p. 103—104° (0·3 g.). From the residues was recovered crude anhydride (3·8 g.).

From **3**:6-*di-tert.-butyl*-1-*naphthoic acid*. The acid (1 g.) was refluxed in quinoline (2 c.c.) in the presence of copper-bronze (0·5 g.) for 30 minutes and the whole was poured into excess of dilute hydrochloric acid. Distillation with steam yielded a solid, m. p. 102—103° (0·45 g.).

The products of the above experiments were crystallised together from alcohol, giving colourless, silky needles, m. p. 102·5—103·5° (Found: C, 90·1; H, 9·85. $C_{18}H_{24}$ requires C, 90·0; H, 10·0%), of **2**:7-*di-tert.-butylnaphthalene*. The *picrate*, prepared in alcoholic solution, was obtained as yellow, microscopic crystals, m. p. 145—145·5° (Found: C, 61·4; H, 5·8; N, 9·05. $C_{18}H_{24}.C_6H_3O_7N_3$ requires C, 61·4; H, 5·8; N, 8·95%).

From naphthalene. The di-*tert.*-butylnaphthalene picrate, m. p. 157—158°, was prepared by the method of Bromby *et al.* (*loc. cit.*) (Found: C, 67·7; H, 6·7; N, 6·6. Calc. for $C_{44}H_{72}O_{14}N_6$: C, 67·2; H, 6·65; N, 7·15%). It was decomposed with 5% aqueous sodium hydroxide and the hydrocarbon, m. p. 82—85°, obtained was repeatedly crystallised from alcohol to give colourless, silky needles, m. p. 102—103°, not depressed on admixture with the **2**:7-di-*tert.*-butylnaphthalene prepared as above.

To a boiling solution of this compound (0·3 g.) in dry alcohol (1·5 c.c.) was added a solution of picric acid (0·3 g.) in the same solvent (1·5 c.c.). The colour deepened to orange and, after a few seconds' boiling, the mixture was allowed to cool. There separated an egg-yolk-coloured compound, m. p. 145—146° (0·5 g.), not depressed on admixture with the **2**:7-di-*tert.*-butylnaphthalene picrate prepared as above.

To a solution of the picrate (0·5 g.) in boiling dry alcohol (5 c.c.) was added di-*tert.*-butylnaphthalene, m. p. 145—146° (0·15 g.), dissolved in the same solvent (3 c.c.). The mixture was boiled for a few seconds and allowed to cool, whereupon orange needles (0·55 g.) crystallised out; m. p. 157—158°, not depressed on admixture with the picrate, m. p. 157—158°, used as the starting material (Found: C, 67·5; H, 6·6; N, 7·35. Calc. for $C_{44}H_{72}O_{14}N_6$: C, 67·2; H, 6·65; N, 7·15%).

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CLOTHWORKERS' RESEARCH LABORATORY,
THE UNIVERSITY, LEEDS.

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149. *The Formation of ββ′-Thiodipropionitrile (Di-2-cyanoethyl Sulphide) and a Study of its Derivatives.*

By J. H. MACGREGOR and C. PUGH.

The formation of ββ′-thiodipropionitrile (di-2-cyanoethyl sulphide) during the reaction of viscose and acrylonitrile and its separation from the reaction mixture at low temperatures are reported. Preparation of the corresponding acid and a number of its derivatives is described. Polycondensation products of the acid and of the derived sulphone with glycols and diamines, such as polyesters and polyamides, have no useful fibre-forming properties.

WHEN acrylonitrile reacts with viscose (a solution of sodium cellulose xanthate in dilute aqueous sodium hydroxide) the viscose changes from its normal golden-brown shade to olive-green within a few minutes (cf. MacGregor and Pugh, *J. Soc. Dyers and Col.*, 1948, **64**, 71). Hollihan and Moss (*Ind. Eng. Chem.*, 1947, **39**, 222) attributed this colour change to the reaction of the acrylonitrile with by-products such as sodium thiocarbonate and sodium sulphide present in the viscose, with formation of ββ′-thiodipropionitrile (di-2-cyanoethyl sulphide), although they did not isolate this product from the reaction mixture.

During a recent investigation (cf. Courtaulds Ltd., MacGregor and Pugh, B.P. Appln. No. 31,659/1947) into the production of partial ethers by treatment of viscose with acrylonitrile at $<16°$ we isolated ββ′-thiodipropionitrile in bulk. With this readily available material we have investigated the production and properties of a number of its derivatives.

Synthesis of ββ′-thiodipropionitrile has been described previously (cf. *e.g.*, Nekrasov, *J. Russ. Phys. Chem. Soc.*, 1927, **59**, 921; D.R.-P. 669,961; Gershbein and Hurd, *J. Amer. Chem. Soc.*, 1947, **69**, 241). Although closely related to mustard gas, it is not vesicant. Hydrolysis with boiling concentrated hydrochloric acid (cf. Nekrasov, *loc. cit.*) produced the corresponding acid, ββ′-thiodipropionic acid (di-2-carboxyethyl sulphide), in almost quantitative yield. The acid is of similar strength to adipic acid ($K_1 = 8{\cdot}4 \times 10^{-6}$ and $K_2 = 2{\cdot}1 \times 10^{-6}$, determined by electrometric titration; cf. Britton, "Hydrogen Ions," London, 1929, p. 144). Various alkyl- and aryl-amides, and esters were prepared by standard methods (cf. Experimental). Oxidation of the acid with bromine water gave a good yield of the corresponding sulphone, which, unlike the parent acid, afforded a crystalline dimethyl ester.

ββ′-Thiodipropionic acid and the derived sulphone were condensed in various ways with ethylene and trimethylene glycols and with hexamethylenediamine (see Experimental), but the fibre-forming properties of the products were not encouraging.

Experimental.

Isolation of ββ′-Thiodipropionitrile.—Viscose (30 kg.), containing 7·75% by wt. of cellulose (1 mol. as anhydroglucose) and 6·2% by wt. of sodium hydroxide and having a " salt index " figure of 5·5, was cooled to 10° and mixed with acrylonitrile (995 c.c., 1·05 mols.). The reaction mixture was stirred at 10—15° for 3 hours and then filtered at 40 lb./sq. in. through one plate (300 sq. in.) of a filter press wrapped with a layer of swansdown and a fine calico filter-cloth. The residue was stirred with water at 15° and filtered at the pump through a Whatman No. 54 filter paper. Washing of the residue with water (at 15°) was continued until the filtrate was free from sodium hydroxide. The crude nitrile was purified (*a*) by recrystallisation by cooling the aqueous solution slowly from 25° to 5° or (*b*) by fusing and heating it to *ca.* 140° (most of the water evaporating) and then filtering it through a Whatman No. 1 filter paper. The clear liquid (230 g.) was allowed to solidify. Recrystallisation of this product from ether gave colourless odourless needles, m. p. 28° (Nekrasov, *loc. cit.*, gives m. p. 24—25°) (Found: N (Kjeldahl), 19·9; S, 22·9. Calc. for $C_6H_8N_2S$: N, 20·0; S, 22·9%).

ββ′-Thiodipropionic Acid.—ββ′-Thiodipropionitrile (180 g.) and concentrated hydrochloric acid (700 c.c.) were shaken vigorously at room temperature and then heated under reflux for 2 hours on a steam-bath. After cooling, the solid was filtered off, washed with cold water, and dried at 105°, giving ββ′-thiodipropionic acid as colourless crystals, m. p. 131—132°. Recrystallisation from water (" Acticarbon ") raised the m. p. to 134° (Nekrasov, *loc. cit.*, gives m. p. 128°) (Found: S, 18·2. Calc. for $C_6H_{10}O_4S$: S, 18·0%). The *disodium* salt, colourless crystals (from ethanol), did not melt below 300° (Found: S, 14·3; Na, 20·7. $C_6H_8O_4SNa_2$ requires S, 14·4; Na, 20·7%). The *bisethylenediamine* salt formed colourless crystals (from ethanol), m. p. 154° (Found: N, 11·6. $C_{14}H_{32}O_4N_4S$ requires N, 11·8%). The *dimethyl* ester, prepared by methanol and sulphuric acid in 90% yield, was a pale straw-coloured liquid, b. p. 158—159°/10 mm., with a rather unpleasant smell (Found: S, 15·2. $C_8H_{14}O_4S$ requires S, 15·5%).

The acid (178 g., 1 mol.) and urea (60 g., 1 mol.) were intimately mixed and heated at 160—170° for 6 hours. Three recrystallisations of the crude product (150 g., 85%) from ethanol (" Acticarbon ") gave the diamide in colourless lustrous plates m. p. 182° (Bennett and Scorah, *J.*, 1927, 194, give m. p. 177—178·5°) (Found: N, 15·8; S, 18·2. Calc. for $C_6H_{12}O_2N_2S$: N, 15·9; S, 18·2%).

When prepared from the diamide (0·05 mol.) and the appropriate alcohol (0·1 mol.), the *didodecyl* and *dihexadecyl* esters formed colourless waxy crystals, m. p. 39° (Found: S, 6·4. $C_{36}H_{74}O_4S$ requires S, 6·2%), and m. p. 53·5° (Found: S, 5·2; $C_{44}H_{90}O_4S$ requires S, 5·1%), from ethanol and acetone respectively (cf. B.P. 592,106).

The diamide (8·8 g., 0·05 mol.) and *n*-dodecylamine (18·5 g., 0·1 mol.), when heated for 5 hours at 170—180°, gave *NN′-di-n-dodecyl-ββ′-thiodipropionamide* as a colourless micro-crystalline substance (from ethanol) with a waxy feel, m. p. 140° (Found: N, 5·4; S, 6·3. $C_{36}H_{72}O_2N_2S$ requires N, 5·5; S, 6·3%).

The *NN-di-n-hexadecyl-amide*, m. p. 131° (Found: N, 4·4. $C_{52}H_{104}O_2N_2S$ requires N, 4·5%), was similarly prepared.

ββ′-Thiodipropionanilide.—Heating ββ′-thiodipropionic acid (8·9 g., 0·05 mol.), aniline (9·3 g., 0·1 mol.), pyridine (10 c.c.), and phosphorus trichloride (6 c.c.) for 4 hours at 115° (cf. Hopper, MacGregor, and Wilson, *J. Soc. Dyers and Col.*, 1939, **55**, 449), and recrystallisation of the product from ethanol (" Acticarbon ") gave the dianilide as colourless crystals, m. p. 165° (Bennett and Scorah, *loc. cit.*, give m. p. 163·5°) (Found: N, 8·4; S, 9·8. Calc. for $C_{18}H_{20}O_2N_2S$: N, 8·5; S, 9·8%).

ββ′-Thiodipropio-p-toluidide.—The *di-p-toluidide* was prepared as above. Recrystallisation from ethanol (" Acticarbon ") gave colourless crystals, m. p. 199° (Found: N, 7·7; S, 9·0. $C_{20}H_{24}O_2N_2S$ requires N, 7·9; S, 9·0%).

ββ′-Thiodipropionanilic Acid.—ββ′-Thiodipropionic acid (17·8 g., 0·1 mol.) and aniline (9·3 g., 0·1 mol.) were heated with fused zinc chloride (2 g.) at 150—160° for 2 hours (cf. Pressman *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1352). The warm, fluid reaction mixture was poured into 220 c.c. of N-sodium hydroxide, and the whole refluxed for 1 hour. The mixture was filtered hot and the filtrate acidified with concentrated hydrochloric acid. This precipitated the monoanilide, which was cooled, filtered at the pump, and washed free from Cl′ and Zn⁺⁺. Recrystallisation from water gave the *acid* as small lustrous plates, m. p. 128° (Found: N, 5·3; S, 12·7%; equiv., 250. $C_{13}H_{17}O_3NS$ requires N, 5·5; S, 12·6%; equiv., 253).

ββ′-Thiodipropio-p-toluidinic acid, prepared similarly, and recrystallised from water, formed fine colourless needles, m. p. 134° (Found: N, 5·2; S, 11·8%; equiv., 263. $C_{14}H_{19}O_3NS$ requires N, 5·2; S, 12·0%; equiv., 267).

Di-(2-carboxyethyl) Sulphone.—ββ′-Thiodipropionic acid (44 g.) was covered with 440 c.c. of water, and 25 c.c. of bromine were added gradually. The reddish-orange solution was set aside at room temperature for 1 hour and then heated on a steam-bath for 30 minutes, filtered hot, and allowed to cool. The solid product was washed with water and dried at 110°; the sulphone (86%) melted at 219—220° (Found: S, 15·0. Calc. for $C_6H_{10}O_6S$: S, 15·2%).

The acid (30·4 g.), methanol (304 c.c.), and concentrated sulphuric acid (15 c.c.) were refluxed for 12 hours and then allowed to cool slowly. The *dimethyl* ester which crystallised was filtered off, pressed dry, washed with dilute sodium carbonate solution, and then water. Recrystallisation from methanol gave a product melting at 115° (Found: S, 13·4. $C_8H_{14}O_6S$ requires S, 13·4%).

Polymers.

Polyesters.—(*a*) ββ′-Thiodipropionic acid (8·9 g.) and ethylene glycol (2·82 c.c., 1·05 mols.) were heated in a metal bath at 190°/15 mm. for 3 hours. A slightly viscous golden liquid was obtained. The liquid was then heated at 220°/2 mm. for 5 hours, giving a golden-yellow viscous oil, insoluble in water.

(*b*) Trimethylene glycol, brought into reaction similarly, gave a highly viscous oil whence very small colourless crystals, m. p. 40°, were obtained by means of acetone and " Acticarbon." The polymers from both glycols yielded no fibres and were probably of relatively low molecular weight.

(*c*) Di-(2-carbomethoxyethyl) sulphone (11·9 g.), ethylene glycol (4·2 g., 1·35 mols.), and anhydrous potassium carbonate (0·01 g.) were heated for 2 hours at 180—200°, then for 2 hours at 220—240°/3 mm. and for 6 hours at 250—260°/3 mm. The product was a dark brown solid, m. p. >285°. Poor fibres could be drawn from the melt.

With lithium methoxide as catalyst, pronounced decomposition of the sulphone occurred at the reaction temperature (280—300°), giving a black porous brittle product.

In both cases, but more markedly with the lithium methoxide catalyst, unpleasant-smelling volatile by-products were obtained.

(*d*) Di-(2-carboxyethyl) sulphone (10·5 g.), ethylene diacetate (10·5 g., 1·44 mols.), and toluene-*p*-sulphonic acid (0·05 g.) were heated for 2 hours at 190—210° in nitrogen, and then for 6·5 hours at 230—240°/1—2 mm. An unpleasant-smelling volatile by-product was detected. The product was a black solid, m. p. *ca.* 320—330° (decomp.), with only a poor fibre-forming capacity.

Polyamides.—(*a*) ββ′-Thiodipropionic acid (17·8 g., 0·1 mol.) and hexamethylenediamine (11·6 g., 0·1 mol.) were heated at 190° for 3 hours and then for a further 3 hours at 220°/2 mm. The product was dissolved in *m*-cresol, and the polymer precipitated as a colourless granular powder by pouring the solution into a large volume of ethanol. The dry powder contained 10·8% of nitrogen, as required by a polymer of $(-HN\cdot[CH_2]_6\cdot NH\cdot CO\cdot[CH_2]_2\cdot S\cdot[CH_2]_2\cdot CO-)_x$. The thiopolyamide had an intrinsic viscosity of 1·1 and yielded poor fibres of low tenacity at 217—226°. The polymer was soluble in *m*-cresol and dimethylformamide and had m. p. ~210° (decomp.). The fibres exhibited dichroic properties.

(*b*) The hexamethylenediamine salt of ββ′-thiodipropionic acid (crystals, m. p. 181—182°, from ethyl alcohol) was prepared by mixing equimolar quantities of the acid and the diamine in 50% aqueous alcohol. The salt was heated at 220—230°/1—2 mm. for 3 hours. The polymer was purified by dissolution in *m*-cresol and pouring into a large volume of ethanol. The precipitated thiopolyamide was a colourless substance which yielded fibres of poor strength but having intrinsic viscosity of 1·2. These fibres and those recorded in the previous paragraph can be "cold-drawn" and give highly crystalline *X*-ray diffraction patterns.

An attempt was made to wet spin the thiopolyamides from *m*-cresol solution, using a hypodermic needle and spinning into 10, 20, 25, and 35% aqueous sodium hydroxide (ethanol was unsatisfactory), 25% appearing to be the most useful concentration. No stretch was put on the fibre as spun. The fibres obtained, however, were excessively brittle and disintegrated on the lightest touch.

(*c*) The salt, m. p. 160°, obtained from di-(2-carboxyethyl) sulphone and hexamethylene diamine, was heated in boiling xylenol through which a stream of nitrogen was passed. In the first run, a black sticky resinous material was obtained, and, in the second, a solid which had not melted at 290° but showed appreciable signs of decomposition.

The authors express their thanks to the Directors of Messrs. Courtaulds Ltd. for permission to publish these results and to their colleague, Dr. E. R. Wallsgrove of Coventry, for preparing the polymers from di-(2-carboxyethyl) sulphone.

MESSRS. COURTAULDS LIMITED, TEXTILE RESEARCH LABORATORY,
BOCKING, BRAINTREE, ESSEX [*Received, November 24th*, 1949.]

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150. *Deoxy-sugars. Part X. Some Methanesulphonyl and Toluene-p-sulphonyl Derivatives of α-Ethyl-2 : 3-dideoxy-D-glucoside.*

By S. LALAND, W. G. OVEREND, and M. STACEY.

The methanesulphonyl and toluene-*p*-sulphonyl esters of α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside and α-ethyl-2 : 3-dideoxy-D-glucoside have been prepared and their exchange reactions with sodium iodide in acetone studied. It has been shown that for the former compound, the ethylenic linkage between $C_{(2)}$ and $C_{(3)}$ exerts an activating influence on substituents at $C_{(4)}$.

IT is well known that when 3 : 4 : 6-triacetyl glucal (I) is heated with water it loses an acetyl group and migration of the ethylenic linkage occurs, the product being 4 : 6-diacetyl φ-glucal (II) (Bergmann, *Annalen*, 1925, **443**, 223). Recently, we used this product as an intermediate in a synthesis of 2-deoxy-D-ribose (Overend and Stacey, *J.*, 1949, 1358) and became interested in the mechanism of this change. The reaction is a fairly general one with acetylated glycals and occurs, not only in the glucose series, but also with galactose (Lohaus and Widmaier, *Annalen*, 1935, **520**, 301) and arabinose derivatives (Gehrke and Aichner, *Ber.*, 1927, **60**, 918).

When D-glucal was boiled with water, under conditions similar to those used for preparing diacetyl φ-glucal from triacetyl glucal there was no migration of the double bond and the initial material was recovered unchanged. In a like manner when D-glucal was heated with water containing acetate ions it underwent no change. However, when glucal was heated under like conditions with acetic acid a reaction did occur and some of the glucal (20%) was converted into 2-deoxy-D-glucose which was isolated from the syrupy reaction product as its dibenzyl mercaptal (Overend, Stacey, and Staněk, *J.*, 1949, 2841). However the main product, which was very labile, was not isolated in crystalline form. From these preliminary experiments it appeared

that the ethylenic linkage between $C_{(1)}$ and $C_{(2)}$ in triacetyl glucal activated the acetyl substituent at $C_{(3)}$ so that gentle heating with water was sufficient to eliminate it, and the acidity consequently developed induced migration of the double bond. Recently, whilst working with methanesulphonyl and toluene-*p*-sulphonyl esters we have obtained some evidence of the activating influence of ethylenic linkages on substituents in molecules of this type.

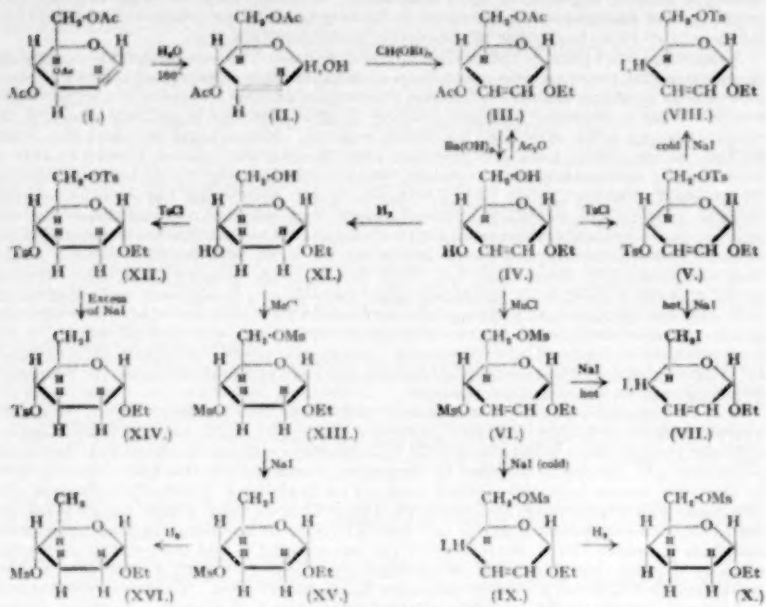
Generally, when a primary hydroxyl group is esterified with a toluene-*p*-sulphonyl or methanesulphonyl residue, the toluene-*p*-sulphonyloxy- or methanesulphonyloxy-group can be exchanged for iodine by the simple expedient of heating with sodium iodide in acetone or in a higher-boiling ketone. When a secondary hydroxyl group in a sugar derivative is similarly esterified, the residues are with a few exceptions not usually replaced. Helferich and Gnüchtel (*Ber.*, 1938, **71**, 712; see also Helferich and Jochinke, *Ber.*, 1940, **73**, 1049) did, however, convert 1 : 2 : 3 : 6-tetra-acetyl 4-methanesulphonyl D-glucose into its corresponding 4-iodo-4-deoxy-derivative by the usual procedure, and a further exception to the general rule was encountered when adjacent primary and secondary hydroxyl groups were esterified with toluene-*p*-sulphonyl residues, since treatment of these esters with sodium iodide in acetone resulted in the elimination of both toluene-*p*-sulphonyloxy-groups and formation of an unsaturated compound (Hahn, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73). The toluene-*p*-sulphonyloxy-residues in the open-chain compounds *iso*mannide and *iso*sorbide (cf. Montgomery and Wiggins, *J.*, 1946, 393) are also exchanged although they are formed by esterification of secondary hydroxyl groups. In these compounds, however, the anhydro-rings may exert some influence. In this communication we describe further instances in unsaturated derivatives of sugars, of the exchange for iodine of methanesulphonyloxy- and toluene-*p*-sulphonyloxy-residues formed by appropriate esterification of secondary hydroxyl groups.

3 : 4 : 6-Triacetyl D-glucal (I) was heated with water and converted into 4 : 6-diacetyl 2 : 3-didehydro-2 : 3-dideoxy-D-glucose (diacetyl ψ-glucal) (II), which was immediately treated with ethyl orthoformate in ethanol to yield 4 : 6-diacetyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (III) previously described by Bergmann (*Annalen*, 1925, **443**, 223). Deacetylation of this with barium hydroxide yielded α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (IV) (Bergmann and Freudenberg, *Ber.*, 1931, **64**, 158). That no other change accompanied this deacetylation was apparent from the fact that (IV) could be acetylated smoothly with acetic anhydride to re-form (III). Moreover, (IV) was non-reducing to lead tetra-acetate in benzene solution, showing that it retained its pyranose structure. It formed a crystalline 4 : 6-*di*-p-*nitrobenzoate* which was a suitable derivative for characterisation. Treatment with toluene-*p*-sulphonyl chloride in dry pyridine afforded crystalline 4 : 6-*ditoluene*-p-*sulphonyl* α-*ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside* (V); similarly with methanesulphonyl chloride a crystalline 4 : 6-*dimethanesulphonyl* derivative (VI) was obtained. When either the ditoluene-*p*-sulphonyl (V) or the dimethanesulphonyl derivative (VI) was heated with excess of sodium iodide in acetone at 110—115° for 3 hours, there was obtained crystalline 4 : 6-*di-iodo* α-*ethyl*-2 : 3-*dehydro*-2 : 3 : 4 : 6-*tetradeoxy*-D-*hexoside* (VII). When, however, the toluene-*p*-sulphonyl derivative (V) was kept for 3 days at 30° with 1·1 moles of sodium iodide in acetone, it gave a monoiodo monotoluene-*p*-sulphonyl derivative (VIII). By analogy with subsequent work this was probably 4-*iodo* 6-*toluene*-p-*sulphonyl* α-*ethyl*-2 : 3-*didehyrod*-2 : 3 : 4-*trideoxy*-D-*hexoside*, but, since it was unstable to the reduction process needed to establish its structure, we concentrated our attention on the corresponding methanesulphonyl derivative which was more stable to this treatment.

When 4 : 6-dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (VI) was kept at 18° for 5 days in the dark with sodium iodide in acetone it yielded 1 mole of sodium methanesulphonate together with a very unstable monoiodo monomethanesulphonyl α-ethyl-hexoside (IX). This rapidly liberated iodine when exposed to light or mild warming and so was immediately hydrogenated. A monomethanesulphonyl α-ethyl-trideoxy-hexoside was obtained. This could be either 6-*methanesulphonyl* α-*ethyl*-2 : 3 : 4-*trideoxy*-D-*glucoside* (X) or 4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside according to whether the methanesulphonyloxy-groups undergoing exchange had been formed by the esterification of a secondary or a primary hydroxyl group respectively. That it was, in fact, the former compound, was demonstrated by synthesising, by an alternative route, the 4-methanesulphonyl derivative, which proved to be different from (X).

Bergmann (*Annalen*, 1925, **443**, 236) showed that when α-ethyl 2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (IV) was reduced it yielded α-ethyl-2 : 3-dideoxy-D-glucoside (XI). This afforded crystalline 4 : 6-*ditoluene*-p-*sulphonyl* and 4 : 6-*dimethanesulphonyl* derivatives (XII and XIII). When (XII) was heated at 110° for 6 hours with excess of sodium iodide in acetone it gave

crystalline *6-iodo 4-toluene-p-sulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside* (XIV). Similarly, when 4 : 6-dimethanesulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside (XIII) and sodium iodide in



(Ts = Toluene-*p*-sulphonyl. Ms = Methanesulphonyl.)

acetone were heated at 110—120° for 6 hours, one mole of sodium methanesulphonate was precipitated and syrupy 6-iodo 4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside (XV) was formed. That these compounds were correctly designated was shown by the fact that further heating with excess of sodium iodide did not result in more exchange; moreover, the conditions employed for the exchange reactions were those designed to effect reaction between sodium iodide and toluene-*p*-sulphonyloxy- or methanesulphonyloxy-residues formed by appropriate esterification of a primary hydroxyl group (see also Overend and Stacey, *J.*, **1949**, 1235; Foster, Overend, Stacey, and Wiggins, *J.*, **1949**, 2542). 6-Iodo 4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside (XV) darkened on being kept for a short time, so it was reduced immediately on isolation by shaking it in an atmosphere of hydrogen with Raney nickel and diethylamine (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, **1946**, **68**, 628). The treatment yielded *4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside* (XVI), which failed to react when heated at 115—120° for 5½ hours with sodium iodide in acetone, thereby indicating that the methanesulphonyl substituent was attached to a secondary hydroxyl group (Overend, Stacey, *et al.*, *loc. cit.*). On the other hand, the compound (X), provisionally designated as 6-methanesulphonyl α-ethyl-2 : 3 : 4-trideoxy-D-glucoside, afforded sodium methanesulphonate (53%; cf. Foster, Overend, Stacey, and Wiggins, *loc. cit.*) when subjected to the same treatment. This result indicated that the methanesulphonyl residue remaining in the compound (X) was attached at $C_{(6)}$ of the sugar.

The interesting fact emerges from this work that, contrary to expectation, when 4 : 6-dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (VI) is kept with sodium iodide in acetone, the methanesulphonyloxy-group formed by exterification of the secondary hydroxyl group exchanges for iodine before that formed by esterification of the primary hydroxyl group. Similar results are obtained with the toluene-*p*-sulphonyl esters of α-ethyl-2 : 3-di-

dehydro-2 : 3-dideoxy-D-glucoside. The ethylenic linkage between $C_{(2)}$ and $C_{(3)}$ clearly confers lability on the substituent on the hydroxyl group of the adjacent carbon atom 4. This is analogous to the elimination of an acetyl group when triacetyl glucal is boiled with water. In this case the acetyl group eliminated is that at $C_{(3)}$ which has an adjacent ethylenic linkage between $C_{(1)}$ and $C_{(2)}$.

Experimental.

4 : 6-*Diacetyl* α-*Ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside*.—3 : 4 : 6-Triacetyl D-glucal (10 g.) and water (200 c.c.) were heated under reflux for 15 minutes. Water was then removed at 40°, and the residue was dried by distilling ethanol over it. A yellow syrup remained which strongly reduced Fehling's solution. This was heated under reflux with ethyl orthoformate (6·4 g.) and absolute ethanol (10 c.c.) for 50 minutes. Ammonium chloride (50 mg.) was added during the reaction. The ethanol and excess of ethyl orthoformate were removed by evaporation *in vacuo*, and the residue crystallised. It recrystallised from 96% ethanol as colourless needles (2·0 g.), m. p. 78—79°, $[\alpha]_D^{17}$ +106·7° (*c*, 2·1 in benzene). Bergmann (*Annalen*, 1925, **443**, 223) reports m. p. 81—82° and $[\alpha]_D^{20}$ +102·7° in benzene for this compound.

α-*Ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside*.—4 : 6-Diacetyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (1·4 g.) was kept with barium hydroxide (3·58 g.) in water (35 c.c.) for 24 hours at room temperature. The excess of barium hydroxide was neutralised with carbon dioxide, and the solution centrifuged. The filtrate was evaporated, and the residue extracted with ethanol (3 × 100 c.c.). Solvent was removed from the extract, and the residue was recrystallised from benzene, forming colourless needles (0·64 g.), m. p. 90—93° (unchanged after repeated recrystallisation). After recrystallisation from ethyl acetate, the m. p. was 94—97°. Sublimation of the material (70°/15 mm.) afforded needles, m. p. 96—97°, $[\alpha]_D^{20}$ +99·5° (*c*, 0·54 in ethanol) (Found : C, 54·95; H, 8·0. Calc. for $C_8H_{14}O_3$: C, 55·2; H, 8·0%). Bergmann and Freudenberg (*Ber.*, 1931, **64**, 158) give m. p. 100—101°, $[\alpha]_D^{20}$ 100·3° in ethanol for this compound. It was not oxidised by lead tetra-acetate in benzene but could be reacetylated with acetic anhydride to yield 4 : 6-diacetyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside in 80% yield.

4 : 6-*Di*-p-*nitrobenzoyl* α-*Ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside*.—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (50 mg.) was dissolved in dry pyridine (0·5 c.c.), and *p*-nitrobenzoyl chloride (130 mg., 2·12 mols.) was added. After 18 hours at room temperature, the solution was poured into water (25 c.c.). The solid which separated was recrystallised from 96% ethanol, and 4 : 6-*di*-p-*nitrobenzoyl* α-*ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside* was obtained as colourless needles (100 mg.), m. p. 129—130°, $[\alpha]_D^{20}$ +109·5° (*c*, 0·66 in benzene) (Found : C, 55·7; H, 4·5; N, 6·1. $C_{22}H_{20}O_{10}N_2$ requires C, 55·9; H, 4·3; N, 5·9%).

4 : 6-*Ditoluene*-p-*sulphonyl* α-*Ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside*.—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·75 g.) was kept at room temperature for 18 hours with toluene-*p*-sulphonyl chloride (0·7 g.) in dry pyridine (0·5 c.c.). The mixture was poured into water, and the precipitated solid filtered off. Recrystallisation from 90% ethanol afforded the *ditoluene*-p-*sulphonyl* derivative (0·12 g.) as colourless needles, m. p. 119—120°, $[\alpha]_D^{18}$ +59° (*c*, 2·16 in benzene) (Found : C, 54·5; H, 5·5; S, 13·0. $C_{32}H_{34}O_9S_2$ requires C, 54·7; H, 5·4; S, 13·2%).

4 : 6-*Dimethanesulphonyl* α-*Ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside*.—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·75 g.), methanesulphonyl chloride (1·15 g., 0·78 c.c.), and dry pyridine (0·5 c.c.) were kept together at 0° for 75 hours. The mixture was worked up in the usual manner, and after recrystallisation from 85% ethanol 4 : 6-*dimethanesulphonyl* α-*ethyl*-2 : 3-*didehydro*-2 : 3-*dideoxy*-D-*glucoside* (0·72 g.) was obtained as colourless needles, m. p. 71—72°, $[\alpha]_D^{20}$ +87·7° (*c*, 1·46 in acetone) (Found : C, 36·4; H, 5·9. $C_{10}H_{18}O_8S_2$ requires C, 36·4; H, 5·5%).

α-*Ethyl*-2 : 3-*dideoxy*-D-*glucoside*.—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·4 g.), dissolved in dry methanol (20 c.c.), was hydrogenated at room temperature in the presence of platinic oxide (100 mg.). The solution was filtered, and the methanol evaporated. The residue crystallised from benzene–light petroleum as colourless needles (0·35 g., 83%), m. p. 67—69° $[\alpha]_D^{20}$ +140·6° (*c*, 0·69 in water) (Found : C, 54·4; H, 8·99. Calc. for $C_8H_{14}O_4$: C, 54·5; H, 9·1%). Bergmann (*loc. cit.*) reports m. p. 72—72·5°, $[\alpha]_D^{18}$ +137·8° in water for this compound.

4 : 6-*Ditoluene*-p-*sulphonyl* α-*Ethyl*-2 : 3-*dideoxy*-D-*glucoside*.—α-Ethyl-2 : 3-dideoxy-D-glucoside (0·25 g.), toluene-*p*-sulphonyl chloride (0·66 g.), and dry pyridine (1·5 c.c.) were kept at room temperature for 60 hours. The mixture was poured into water, and the product isolated in the usual manner. After recrystallisation from ethanol 4 : 6-*ditoluene*-p-*sulphonyl* α-*ethyl*-2 : 3-*dideoxy*-D-*glucoside* (0·5 g.) was obtained as colourless needles, m. p. 58—60°, $[\alpha]_D^{20}$ +85° (*c*, 0·89 in benzene) (Found : C, 54·6; H, 5·9. $C_{32}H_{34}O_8S_2$ requires C, 54·5; H, 5·8%).

4 : 6-*Dimethanesulphonyl* α-*Ethyl*-2 : 3-*dideoxy*-D-*glucoside*.—α-Ethyl-2 : 3-dideoxy-D-glucoside (0·3 g.), methanesulphonyl chloride (0·32 c.c.), and dry pyridine (0·5 c.c.) were kept at 0° for 12 hours. The mixture was then poured into water, and the oil which separated was extracted with chloroform. The extract was washed with dilute sulphuric acid (2%) and then water, and dried ($MgSO_4$). Evaporation of the solvent yielded a syrup which crystallised when triturated with water. Recrystallisation of the solid from 90% ethanol yielded the *dimethanesulphonyl* derivative (0·14 g.) as colourless needles, m. p. 68—69°, $[\alpha]_D^{20}$ +118·7° (*c*, 1·11 in acetone) (Found : C, 36·4; H, 5·8. $C_{10}H_{20}O_8S_4$ requires C, 36·2; H, 6·0%).

6-*Iodo* 4-*Toluene*-p-*sulphonyl* α-*Ethyl*-2 : 3 : 6-*trideoxy*-D-*glucoside*.—4 : 6-Ditoluene-*p*-sulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside (0·3 g.), sodium iodide (0·252 g.), and dry acetone (12 c.c.) were heated in a sealed tube at 110° for 6 hours. Sodium toluene-*p*-sulphonate was precipitated. This was collected by filtration, washed with anhydrous acetone, dried, and weighed (0·130 g. = 100% replacement of one toluene-*p*-sulphonyl group). The acetone solution was evaporated, and the residue treated with chloroform and water. The chloroform layer was washed with dilute sodium thiosulphate solution, dried ($MgSO_4$), and evaporated. The residue slowly crystallised and was recrystallised from 80% ethanol. 6-*Iodo* 4-*toluene*-p-*sulphonyl* α-*ethyl*-2 : 3 : 6-*trideoxy*-D-*glucoside* (0·2 g.) was obtained as

colourless needles, m. p. 58—59°, $[\alpha]_D^{20}$ +88·8° (*c*, 0·39 in benzene) (Found: C, 40·3; H, 5·2; I, 29·1. $C_{13}H_{21}O_5SI$ requires C, 40·8; H, 4·9; I, 28·8%).

4 : 6-*Di-iodo* α-*Ethyl*-2 : 3-*dideoxy*-2 : 3 : 4 : 6-*tetradeoxy*-D-*hexoside*.—(*a*) **4 : 6**-Ditoluene-*p*-sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·72 g.) and dry sodium iodide (0·6 g.) in dry acetone (17 c.c.) were heated together at 110—115° for 3 hours. (Milder exchange conditions yielded only syrupy products.) The amount of sodium toluene-*p*-sulphonate formed (0·55 g.), after filtration, washing with acetone and drying, corresponded to 93% replacement of both toluene-*p*-sulphonyl residues. The acetone was evaporated, and the residue extracted with chloroform (50 c.c.). The extract was washed with dilute sodium thiosulphate solution and dried ($MgSO_4$). After evaporation of the chloroform, the residue partly crystallised. This was recrystallised from 80% ethanol and **4 : 6-*di-iodo* α-*ethyl*-2 : 3-*didehydro*-2 : 3 : 4 : 6-*tetradeoxy*-D-*hexoside*** (0·12 g.) was obtained as colourless needles, m. p. 97—98°, $[\alpha]_D^{20}$ −364·8° (*c*, 1·88 in chloroform) (Found: C, 24·6; H, 3·1; I, 63·1. $C_8H_{12}O_3I_2$ requires C, 24·3; H, 3·0; I, 63·5%). This compound was very unstable, and iodine was liberated even after 1 day in the dark. Decomposition was complete in 10 days.

(*b*) **4 : 6**-Dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·3 g.), sodium iodide (0·3 g.), and dry acetone were heated at 105—110° for 3 hours. The sodium methanesulphonate formed corresponded to 93% replacement of both methanesulphonyl groups. The product was isolated as above but showed no tendency to crystallise. It was dissolved in benzene (10 c.c.) and run through a short column of alumina, which was then washed with benzene (20 c.c.); 5 c.c. portions (*a*, *b*, *c*, and *d*) were collected; (*a*), (*c*), and (*d*) when evaporated gave syrupy products, but (*b*) yielded crystals which recrystallised from 80% ethanol (0·0279 g.) as colourless needles, m. p. 97—98° alone or in admixture with the di-iodo-compound described above.

4-*Iodo* 6-*Toluene*-p-*sulphonyl* α-*Ethyl*-2 : 3-*didehydro*-2 : 3 : 4-*trideoxy*-D-*hexoside*.—**4 : 6**-Ditoluene-*p*-sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·5 g.), dry acetone (15 c.c.), and dry sodium iodide (0·175 g. = 1·1 mols.) were kept in a stoppered flask, protected from light, at 18° for 9 days. The reaction mixture became yellow owing to liberated iodine, and sodium toluene-*p*-sulphonate (0·15 g. = 75% replacement of one toluene-*p*-sulphonyloxy-group) was precipitated (Found: C, 43·3; H, 3·6. Calc. for $C_7H_7O_3SNa$: C, 43·4; H, 3·6%).

After separation of this salt, the acetone was evaporated, and the residue extracted with chloroform. After being washed with 1% sodium thiosulphate, the extract was dried ($MgSO_4$) and the solvent evaporated. The only crystalline material which could be isolated from the residue was unchanged **4 : 6**-ditoluene-*p*-sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·04 g.), m. p. 119—120°. If the temperature at which the exchange was carried out was raised to 25°, then sodium toluene-*p*-sulphonate equivalent to 83% replacement was obtained. At 30°, however, complete replacement was effected. The unsaturated ditoluene-*p*-sulphonyl derivative (0·2 g.), sodium iodide (0·061 g.), and dry acetone (5·5 c.c.) were kept together in a stoppered flask protected from light at 30° for 3 days. The product was isolated in the usual manner and a syrup was obtained (0·146 g.). This was purified by passage through a column of alumina, and a straw-coloured syrup (0·096 g.) was obtained: $[\alpha]_D^{20}$ −59·6° (*c*, 1·5 in benzene) (Found: C, 40·9; H, 4·4; OEt, 9·96. $C_{11}H_{19}O_5SI$ requires C, 41·1; H, 4·3; OEt, 10·28%). This syrupy *compound* was unstable and on storage liberated much iodine in 2 days. Attempts to hydrogenate the ethylenic linkage resulted in the uptake of more than 1 mol. of hydrogen even at room temperature.

6-*Methanesulphonyl* α-*Ethyl*-2 : 3 : 4-*trideoxy*-D-*glucoside*.—**4 : 6**-Dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·595 g.), sodium iodide (0·29 g. = 1·2 mols.), and dry acetone (10 c.c.) were kept together at 18° for 5 days in absence of light. Sodium methanesulphonate (0·19 g.) separated and was removed by filtration. The product was isolated in the usual manner (0·60 g.) and purified by passage through a column of alumina. A syrup was obtained which was very unstable and sensitive to light and mild heating. It readily liberated iodine and so, as soon as it was isolated, it was hydrogenated in methanol (15 c.c.) containing diethylamine (0·36 c.c.) and a trace of water. Raney nickel was used as catalyst and the mixture was shaken at room temperature for 3·5 hours in an atmosphere of hydrogen at 20 mm. over-pressure. The solution was filtered, and the solvent evaporated. The residue was treated with chloroform and water. The aqueous layer gave a strong positive test for iodide ions. The chloroform layer was dried ($MgSO_4$), and the solvent evaporated. A pale yellow syrup remained (0·33 g.) which gave a positive test for sulphur and a negative test for iodine and had $[\alpha]_D^{20}$ +65·3° (*c*, 2·45 in acetone). It was **6-*methanesulphonyl* α-*ethyl*-2 : 3 : 4-*trideoxy*-D-*glucoside*** (Found: C, 45·4; H, 7·3; S, 12·8. $C_8H_{16}O_5S$ requires C, 45·4; H, 7·5; S, 13·4%).

4-*Methanesulphonyl* α-*Ethyl*-2 : 3 : 6-*trideoxy*-D-*glucoside*.—**4 : 6**-Dimethanesulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside (0·13 g.) and sodium iodide (in dry acetone (0·07 g. in 10 c.c.) were heated at 115—120° for 6 hours. Separation of sodium methanesulphonate (0·044 g. = 95·6% replacement of 1 methanesulphonyloxy-group) commenced immediately, and replacement seemed easier to effect than with toluene-*p*-sulphonyl esters. The solid was filtered off, and the filtrate was evaporated to dryness. Water and chloroform were added to the residue, and the chloroform layer was separated, washed (dilute sodium thiosulphate solution), and dried ($MgSO_4$). Evaporation of the solvent afforded some syrup, which was dissolved in methanol (10 c.c.) containing diethylamine (0·1 c.c.) and shaken with Raney nickel in an atmosphere of hydrogen at a slight over-pressure. When the uptake of hydrogen ceased, the solution was filtered and evaporated. The residue was treated with water and chloroform. The aqueous layer gave a strong positive test for iodide ions. The chloroform layer was dried ($MgSO_4$), and the solvent evaporated. A yellow syrup (0·087 g.) remained which was free from iodine. It was **4-*methanesulphonyl* α-*ethyl*-2 : 3 : 6-*trideoxy*-D-*glucoside***, $[\alpha]_D^{20}$ +122·9° (*c*, 2·17 in acetone) (Found: C, 46·1; H, 7·5; OEt, 18·7. $C_8H_{16}O_5S$ requires C, 45·4; H, 7·5; OEt, 18·9%).

Exchange Experiments.—(*a*) **4**-Methanesulphonyl α-ethyl-2 : 3 : **6**-trideoxy-D-glucoside (0·063 g.) was heated with sodium iodide (0·063 g.) in dry acetone (7·0 c.c.) at 115—120° for 5½ hours. No sodium methanesulphonate was formed and the initial materials could be recovered. (*b*) **6**-Methanesulphonyl α-ethyl-2 : 3 : 4-trideoxy-D-glucoside (0·178 g.) and sodium iodide (0·12 g.) in acetone (9 c.c.) were heated together under identical conditions. Sodium methanesulphonate (0·047 g.) was precipitated

and was collected, washed with dry acetone, dried, and weighed. It corresponded to 53% replacement of the methanesulphonyloxy-residue in the initial material.

Experiments with Glucal.—(a) Glucal (1 g.) was boiled with water (12 c.c.) for 15 minutes. There was no change in optical rotation ($[\alpha]_D$ −7·5°) and the D-glucal could be recovered unchanged.[10] (b) Glucal (0·5 g.) was dissolved in water (6 c.c.) containing crystalline sodium acetate (0·5 g.), and the solution boiled for 20 minutes. There was no change in optical rotation, and the solution developed no reducing power to Fehling's solution. (c) Glucal (1·08 g.) was dissolved in water (40 c.c.) containing acetic acid (0·040 g.), and the solution boiled. The change in optical rotation was followed polarimetrically:

Time (mins.)	0	20	40	60	80
$[\alpha]_D^{20}$	−7·8°	+3·9°	+10·4°	+16·6°	+16·6°

The solution soon rapidly restored the colour to Schiff's reagent. After neutralisation and evaporation, toluene-α-thiol was added to the syrup together with concentrated hydrochloric acid. The product was isolated as described by Overend, Stacey, and Stanek (*J.*, 1949, 2841) and 2-deoxy-D-glucose dibenzyl mercaptal (20%), m. p. 147—148°, was obtained but no derivative of 2 : 3-didehydro-2 : 3-deoxy-D-glucose.

Certain of the analyses were carried out by Drs. Weiler and Strauss (Oxford). Our thanks are due to the British Empire Cancer Campaign (Birmingham Branch) for financial assistance. One of us (S. L.) thanks the University of Oslo for the award of a Familien Stiliesen's grant which enabled him to take part in this work.

CHEMISTRY DEPARTMENT,
THE UNIVERSITY, BIRMINGHAM, 15. [*Received, December 10th*, 1949.]

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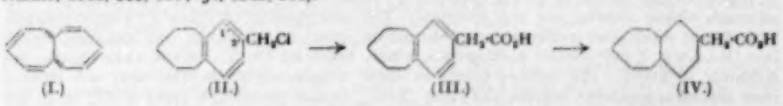
151. *Attempts to Prepare New Aromatic Systems. Part II. Heptalene.*

By G. O. ASPINALL and WILSON BAKER.

Experiments were directed towards the synthesis of heptalene (I). Benzocycloheptene is converted through its 2'-chloromethyl derivative (II) into the fully saturated aminomethyl compound (V), which yields by the Demjanov reaction a 3-hydroxydodecahydroheptalene and a decahydroheptalene (VI). Attempts to effect catalytic dehydrogenation of (VI) have been unsuccessful.

In model experiments leading to the hydroazulene series ethyl 3-2-ketocyclopentylvalerate (VIII) has been converted into the ketones (XI) and (XII).

THE possibility that a bicyclic, unsaturated hydrocarbon of aromatic type possessing two fused seven-membered rings might be prepared was first mentioned by Baker (*J.*, 1945, 264). This substance (I), for which the name heptalene has been used by one of us on numerous occasions since 1944, is a ring homologue of azulene, and the present experiments were begun with the object of attempting to prepare this hydrocarbon. Partly because collaboration between the authors is no longer possible, and partly because others have started work in this series (Horn and Rapson, *Nature*, 1947, **160**, 829; *J.*, 1949, 2421; see also Büchi and Jeger, *Helv. Chim. Acta*, 1949, **32**, 538, who have described the synthesis of certain derivatives of 5 : 5 : 0-*bicyclo*dodecane), it is thought desirable to publish our experiments so far as they have progressed. There is as yet no factual information as to the existence or non-existence of compounds of the "aromatic" heptalene type, although some calculations have been made in the attempt to assess the probable stability of such a conjugated system (Craig and Maccoll, *Nature*, 1948, **161**, 481; *J.*, 1949, 964).



(I.) (II.) (III.) (IV.) (V.) (VI.) (VII.)

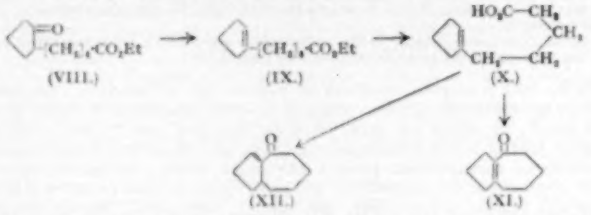
The present synthetical method starts from benzocycloheptene (benzsuberane) and uses the Demjanov reaction for the enlargement of the finally reduced six-membered ring; it is analogous to a synthesis of azulene from indane described by Arnold (*Ber.*, 1943, **76**, 777; cf. also Plattner, Fürst, and Studer, *Helv. Chim. Acta*, 1947, **30**, 1091). Chloromethylation of benzocycloheptene

yielded *2'-chloromethylbenzocycloheptene* (II) which is orientated by analogy, and this was then converted into, successively, *2'-cyanomethylbenzocycloheptene* and the homogeneous, crystalline *benzocycloheptene-2'-acetic acid* (III). The *ethyl* ester of (III) was reduced with hydrogen in presence of Adams's platinum oxide catalyst to *ethyl* cyclo*hexano*cyclo*heptane-2'-acetate*, hydrolysis of which yielded an almost homogeneous cyclo*hexano*cyclo*heptane-2'-acetic acid* (IV). Application of the von Auwers–Skita rule (von Auwers, *Annalen*, 1920, **420**, 84; Skita, *Ber.*, 1920, **53**, 1792) suggests that the acid (IV) probably possesses the *cis*-configuration of the two rings. Treatment of this acid with sodium azide under the conditions of the Schmidt reaction then gave *2'-aminomethylcyclohexanocycloheptane* (V), characterised as the crystalline *benzoyl* derivative. The action of nitrous acid on (V) yielded an unsaturated hydrocarbon, probably the Δ^1-*decahydroheptalene* (VI), and an alcohol, probably 3-hydroxydodecahydroheptalene (VII), which was not obtained pure.

A few attempts have been made to dehydrogenate decahydroheptalene (VI) over palladium–charcoal at 310—330°/14 mm.; the product, a colourless oil, possessed a higher refractive index than (VI) and was unsaturated, but did not yield a picrate. The lengthy synthetical processes involved in the preparation of the aminomethyl compound (V) have allowed the final reactions which might lead to the synthesis of heptalene to be performed only on a very small scale.

A second projected synthesis of heptalene involved the formation of a seven-membered ring by the cyclodehydration of a suitable unsaturated acid, as in (X). This method has now, however, been described by Büchi and Jeger (*loc. cit.*), who started from a *cyclo*heptane derivative, but our preliminary experiments to test the feasibility of this approach started from a *cyclo*pentane and led to the reduced azulene series.

Ethyl *cyclo*pentanone-2-carboxylate was condensed with ethyl 4-iodovalerate giving *ethyl* 4-(*2-keto-1-carbethoxycyclopentyl*)*valerate*, which was simultaneously hydrolysed and decarboxylated, and then esterified, yielding *ethyl* 4-*2-ketocyclopentylvalerate* (VIII). The ketone (VIII) was then reduced by the Meerwein–Ponndorf method to the secondary alcohol, and dehydrated with thionyl chloride to the unsaturated ester, probably mainly *ethyl* 4-cyclo-



pent-1-enylvalerate (IX). Hydrolysis of (IX) yielded the corresponding acid (X) (uncharacterised), which was cyclised (*a*) by treatment of the acid chloride with stannic chloride in carbon disulphide (method due to Cook and Lawrence, *J.*, 1935, 1637), and (*b*) by treatment of the free acid with zinc chloride in acetic acid–acetic anhydride (method due to Bachmann and Dreiding, *J. Org. Chem.*, 1948, **13**, 324). Both cyclisation procedures yielded small quantities of liquid ketonic products giving deep-red 2 : 4-*dinitrophenylhydrazones*, $C_{16}H_{18}O_4N_4$, which although closely similar are not identical. The non-identity of these 2 : 4-dinitrophenylhydrazones, which give no depression of the melting point on admixture, was confirmed by the fact that their *X*-ray powder photographs, kindly taken by Dr. T. Malkin, were slightly but definitely different. The intense colour of these compounds shows that they are derived from the $\alpha\beta$-unsaturated ketones (XI) and (XII). Should the olefinic bond in (X) be in the alternative position cyclisation might theoretically give rise to a *bicyclo*[5 : 2 : 1]decenone with an eight-membered ring, but this is considered improbable. The liquid ketone (XI) was first prepared by Hückel and Schnitzpahn by internal condensation of 1 : 6-diketo*cyclo*decane (*Annalen*, 1933, **505**, 274) and characterised by means of its crystalline oxime. We have been unable to obtain a solid oxime from either of our ketones, and it has thus been impossible to confirm the identity of their ketone previously described with either of ours.

During the course of this work we had occasion to make *trans-cyclo*pentane-1 : 2-dicarboxylic acid. This acid has previously been made from trimethylene dibromide *via* trimethylenebismalonic ester, cyclisation of the related disodio-derivative by treatment with bromine, and

finally hydrolysis and decarboxylation (Perkin, *J.*, 1887, **51**, 240; 1894, **65**, 584; Uschakov, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 795; Kon and Nandi, *J.*, 1933, 1628; Guha and Seshriengar, *Ber.*, 1936, **69**, 1212). We find that the acid is more conveniently prepared from the readily available ethyl *cyclo*pent-1-enylcarboxylate (from *cyclo*pentanone cyanohydrin by dehydration and simultaneous hydrolysis and esterification; Cook and Linstead, *J.*, 1934, 959), by addition of the elements of hydrogen cyanide to the double bond, and hydrolysis of the cyano-ester. The *diamide* and *dinitrile* of *trans-cyclo*pentane-1 : 2-dicarboxylic acid are described.

Experimental.

Preparation of δ-Phenylvaleric Acid from 3-Phenylpropyl Bromide.—3-Phenylpropyl alcohol (136 g.) was refluxed for 4 hours with 48% hydrobromic acid (480 g.), the mixture cooled, diluted, and extracted with ether, and the extract washed with aqueous sodium carbonate, dried, and distilled, giving the bromide (170 g., 82%), b. p. 107—110°/8—9 mm. The procedure of Norris, Watt, and Thomas (*J. Amer. Chem. Soc.*, 1916, **38**, 1078) gives a 63% yield. Condensation of this bromide (80 g.) with ethyl malonate (von Braun and Kruber, *Ber.*, 1912, **45**, 386) gave ethyl 3-phenylpropylmalonate (70 g.; b. p. 180—195°/13 mm.), hydrolysis and decarboxylation of which gave finally δ-phenylvaleric acid, which after recrystallisation from light petroleum (b. p. 60—80°) had m. p. 57° (lit., 61°) (yield 30 g.).

Preparation of δ-Phenylvaleric Acid from Cinnamylidenemalonic Ester.—Cinnamaldehyde (82·5 g.), ethyl malonate (100 g.), benzene (200 c.c.), and piperidine (5 c.c.) were refluxed and slowly distilled till the calculated amount of water had collected (7½ hours). After cooling of the mixture, benzene (100 c.c.) was added and the solution washed successively with water, dilute hydrochloric acid, and sodium hydrogen carbonate solution, dried, and distilled, giving ethyl cinnamylidenemalonate, b. p. 188—190°/7 mm. (126 g.). Hydrolysis of this ester (172 g.) was effected by boiling aqueous sodium hydroxide (230 g. in 700 c.c.) (8—9 hours); water (500 c.c.) was then added, reduction carried out with Raney nickel alloy as described by Cook, Philip, and Somerville (*J.*, 1948, 164), and the resulting saturated acid decarboxylated, giving finally δ-phenylvaleric acid which, after purification as before, was obtained in colourless crystals, m. p. 60° (70 g.).

1 : 2-*Benz*cyclo*heptен*-3-*one*.—The following method is based on that of Plattner (*Helv. Chim. Acta*, 1944, **27**, 804): it is carried out much more rapidly in almost twice the concentration but gives the same yield of benz*cyclo*heptenone. δ-Phenylvaleryl chloride (19·5 g.) in carbon disulphide (200 c.c.) was added (4 hours) to a stirred refluxing mixture of aluminium chloride (27·5 g.) and carbon disulphide (200 c.c.), and stirring was continued for 6 hours, after which the solvent was removed by distillation and the residue poured on ice (500 g.) and steam-distilled. The benz*cyclo*heptenone, isolated from the distillate by means of ether, was a liquid, b. p. 128—130°/6—7 mm. (14·0 g.).

2'-*Chloromethylbenz*cyclo*heptene* (II).—Benz*cyclo*heptene (56 g.), aqueous formaldehyde (35 c.c.; 40% solution), and concentrated hydrochloric acid (77 c.c.) were stirred vigorously at 60—70°, concentrated sulphuric acid (52 c.c.) was added dropwise during 7 hours, and stirring continued for a further 20 hours at the same temperature. The cooled mixture was then diluted with water and extracted with ether, and the extracts were washed with sodium hydrogen carbonate solution, dried, and distilled, giving two main fractions, (1) b. p. 60—120°/6 mm. (15 g.) consisting mainly of benz*cyclo*heptene, and (2) b. p. 120—133°/6 mm. (46 g.). Redistillation of fraction (2) gave 2'-*chloromethylbenz*cyclo*heptene* (II) (40 g.), b. p. 138—141°/9 mm., n_D^{25} 1·5672 (Found: C, 73·8; H, 7·0; Cl, 18·7. $C_{12}H_{11}Cl$ requires C, 74·0; H, 7·7; Cl, 18·3%).

2'-*Cyanomethylbenz*cyclo*heptene*.—To (II) (35 g.) in ethanol (200 c.c.) was added a solution of potassium cyanide (23 g.) in water (50 c.c.), and the mixture refluxed for 5 hours. Dilution with water and extraction with ether yielded 2'-*cyanomethylbenz*cyclo*heptene* (28 g.) as a colourless oil, b. p. 155—170°/10 mm., n_D^{25} 1·5518 (Found: C, 84·0; H, 8·1; N, 7·6. $C_{13}H_{13}N$ requires C, 84·3; H, 8·1; N, 7·6%).

*Benz*cyclo*heptene*-2'-*acetic Acid* (III).—2'-Cyanomethylbenz*cyclo*heptene (28 g.) was refluxed for 2 hours with water (25 c.c.), concentrated sulphuric acid (25 c.c.), and glacial acetic acid (25 c.c.). The mixture was diluted with water and extracted with ether, the extracts were shaken with dilute sodium hydroxide, the alkaline layer was acidified, and the precipitated *benz*cyclo*heptene*-2'-*acetic acid* (III) crystallised from aqueous acetic acid and then twice from light petroleum (b. p. 60—80°), giving fine needles (10·3 g.), m. p. 127° (Found: C, 76·6; H, 7·7. $C_{13}H_{14}O_2$ requires C, 76·5; H, 7·8%). The *anilide* was prepared by heating the acid (1 g.) with thionyl chloride (1 c.c.) under reflux till reaction was complete, diluting the mixture with ether, and adding aniline (1 g.) slowly with cooling; the ethereal solution, after being washed with dilute hydrochloric acid, yielded a solid which when crystallised three times from benzene–light petroleum (b. p. 60—80°) gave fine, silky needles, m. p. 142—143° (Found: C, 81·3; H, 7·4; N, 5·4. $C_{19}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

*Ethyl Benz*cyclo*heptene*-2'-*acetate*.—(*a*) The preceding acid (10 g.) was refluxed with ethanol (100 c.c.) and concentrated sulphuric acid (3 c.c.) for 4 hours and the *ester* isolated in the usual way as a colourless oil (10·4 g.), b. p. 151—154°/4 mm., n_D^{17} 1·5282 (Found: C, 77·5; H, 8·7. $C_{15}H_{18}O_2$ requires C, 77·6; H, 8·6%).

(*b*) 2'-Cyanomethylbenz*cyclo*heptene (28 g.) was refluxed for 18 hours with ethanol (105 c.c.) and concentrated sulphuric acid (10 c.c.), excess of ethanol removed under diminished pressure, water added, and the mixture extracted with ether. After being shaken with sodium hydrogen carbonate solution and drying, the ethereal layer yielded the ester (25 g.), b. p. 165—167°/9 mm.

Hydrolysis of the ester (25 g.) by boiling with potassium hydroxide (20 g.), water (20 c.c.), and ethanol (20 c.c.) for 4 hours yielded the free acid (III) which, after twice crystallising from dilute acetic acid and once from light petroleum (b. p. 60—80°), formed needles (13·2 g.), m. p. 127°.

Ethyl cyclo*Hexano*cyclo*heptane*-2'-*acetate*.—Ethyl benz*cyclo*heptene-2'-acetate (10·4 g.) in glacial acetic acid (100 c.c.) was shaken in hydrogen at atmospheric pressure in presence of Adams's platinum oxide catalyst (0·5 g.), rather more than the theoretical volume of hydrogen being absorbed in 72 hours.

After filtration the bulk of the solvent was removed under diminished pressure, the residue shaken with water and ether, and the ethereal layer shaken with sodium carbonate solution, dried, and distilled. *Ethyl* cyclo*hexano*cyclo*heptane-2'-acetate* was obtained as a colourless liquid (10·2 g.), b. p. 146—148°/4 mm., n_D^{15} 1·4826 (Found: C, 76·0; H, 10·8. $C_{15}H_{26}O_2$ requires C, 75·6; H, 10·9%).

(*cis-?*)cyclo*Hexano*cyclo*heptane-2'-acetic Acid* (IV).—The preceding ester (36 g.) was refluxed for 4 hours with potassium hydroxide (16 g.), water (40 c.c.), and ethanol (40 c.c.). After dilution, extraction with ether, and acidification, the semi-solid mass was collected and crystallised twice from light petroleum (b. p. 60—80°), giving cyclo*hexano*cyclo*heptane-2'-acetic acid* (IV) (11·5 g.) as small leaflets, m. p. 92—93°, unaltered by further crystallisation (Found: C, 74·4; H, 10·6. $C_{13}H_{22}O_2$ requires C, 74·3; H, 10·5%). The light petroleum mother-liquors yielded a further quantity of the acid, b. p. 169—171°/0·5 mm. (9·5 g.), which crystallised on storage.

*2'-Aminomethylcyclohexano*cyclo*heptane* (V).—*cyclo*Hexano*cyclo*heptane-2'-acetic acid (9·5 g.), dissolved in concentrated sulphuric acid (18 c.c.), was covered with a layer of chloroform (90 c.c.) and vigorously stirred while sodium azide (3·6 g.) was slowly added. Stirring was then continued whilst the temperature was raised to 45°, and after evolution of gas was complete the mixture was poured on ice, made alkaline with sodium hydroxide, and extracted with ether. The extract yielded *2'-aminomethylcyclohexano*cyclo*heptane* (V) as an oil (7·1 g.), b. p. 108—110°/3 mm., n_D^{15} 1·5016 (Found: C, 79·7; H, 12·8; N, 7·6. $C_{13}H_{25}N$ requires C, 79·6; H, 12·7; N, 7·7%). The *benzoyl* derivative, prepared by the Schotten–Baumann technique, was crystallised 3 times from aqueous ethanol and obtained as thin hexagonal plates, m. p. 129—131° (Found: C, 80·0; H, 9·7; N, 4·6. $C_{20}H_{27}ON$ requires C, 80·0; H, 9·5; N, 4·6%).

*Action of Nitrous Acid on 2'-Aminomethylcyclohexano*cyclo*heptane* (V). *Decahydroheptalene* (VI).—To the aminomethyl compound (V) (7·1 g.), dissolved in glacial acetic acid (3·5 c.c.) and water (70 c.c.), was added sodium nitrite (4·2 g.) in water (28 c.c.), and the mixture then heated on the water-bath until evolution of nitrogen had ceased. The oil which separated was extracted with ether, the extracts were washed with aqueous sodium hydroxide, dried, and distilled, giving two main fractions: (*a*) b. p. 53—93°/0·5 mm. (1·5 g.), and (*b*) b. p. 105—115°/1 mm., n_D^{15} 1·5022 (3·6 g.). Redistillation of fraction (*a*) over sodium gave *decahydroheptalene* (VI) as a colourless oil (1·0 g.), b. p. 58—62°/0·5 mm., n_D^{15} 1·5005, which became slightly brown when kept (Found: C, 87·2; H, 12·3. $C_{13}H_{20}$ requires C, 87·8; H, 12·1%). Fraction (*b*) probably consists mainly of 3-hydroxydodecahydroheptalene (VII) (Found: C, 77·8; H, 11·6. $C_{13}H_{24}O$ requires C, 79·1; H, 12·1%).

Ethyl δ-(2-Keto-1-carbethoxycyclopentyl)valerate.—Ethyl 2-ketocyclopentane-1-carboxylate (24 g.) was added to powdered sodium (3·5 g.) and dry toluene (200 c.c.), and the mixture stirred till evolution of hydrogen had ceased (*ca.* 2 hours). Freshly distilled ethyl δ-iodovalerate (39 g.; Carter, *J. Amer. Chem. Soc.*, 1928, **50**, 1967) was then added, and the mixture stirred and refluxed for 16 hours. Water was added, and the toluene layer separated, washed with dilute sodium hydroxide solution, dried, and distilled, yielding *ethyl δ-(2-keto-1-carbethoxycyclopentyl)valerate* as a colourless oil (28 g.), b. p. 180—182°/4 mm. (Found: C, 63·6; H, 8·7. $C_{15}H_{24}O_5$ requires C, 63·4; H, 8·5%). This ester did not yield a crystalline 2 : 4-dinitrophenylhydrazone.

Ethyl δ-2-Ketocyclopentylvalerate (VIII).—The preceding ester (25 g.) was refluxed for 8 hours with concentrated hydrochloric acid (50 c.c.), diluted, and extracted with ether. The extract (*A*) was shaken with excess of dilute aqueous sodium hydroxide. The alkaline layer yielded to ether crude δ-2-ketocyclopentylvaleric acid (7·6 g.) as an oil which failed to crystallise, but which readily gave a 2 : 4-*dinitrophenylhydrazone* which was crystallised 5 times from benzene–light petroleum (b. p. 60—80°) and obtained as orange plates, m. p. 145—146° (Found: C, 53·4; H, 5·8; N, 15·6. $C_{17}H_{24}O_6N_4$ requires C, 52·7; H, 5·5; N, 15·4%). The crude acid (7·4 g.) was refluxed for 4 hours with ethanol (100 c.c.) and concentrated sulphuric acid, and the ester isolated in the usual way, combined with that remaining in the ethereal extract (*A*), and distilled, yielding *ethyl δ-2-ketocyclopentylvalerate* (VIII) (14·6 g.) as an oil, b. p. 124—125°/1·5 mm., $n_D^{17.5}$ 1·4567 (Found: C, 67·2; H, 9·9. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%). The 2 : 4-*dinitrophenylhydrazone* of this ester after crystallising twice from ethanol and once from methanol formed fine, orange-yellow plates, m. p. 78—79° (Found: C, 55·0; H, 6·1; N, 14·0. $C_{18}H_{24}O_6N_4$ requires C, 55·1; H, 6·1; N, 14·3%).

Ethyl δ-2-Hydroxycyclopentylvalerate.—To a solution of aluminium *iso*propoxide, made from aluminium foil (3·1 g.) and *iso*propyl alcohol (34 c.c.) by refluxing with a trace of mercuric chloride and carbon tetrachloride for 6 hours, was added ethyl δ-2-keto*cyclo*pentylvalerate (VIII) (8·1 g.) in *iso*propyl alcohol (50 c.c.). The mixture was refluxed and allowed to distil very slowly while *iso*propyl alcohol was added at the same rate; after 6 hours the distillate was free from acetone, and the solvents were then removed from the reaction mixture under diminished pressure. The product was then acidified with dilute hydrochloric acid and yielded to ether ethyl δ-2-hydroxy*cyclo*pentylvalerate as an oil (6·8 g.), b. p. 145—150°/4 mm. (Found: C, 69·1; H, 11·0. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%). This ester is not entirely homogeneous and probably contains some of the related unsaturated ester (below), and there is also the possibility of some ester exchange with the *iso*propyl alcohol.

*Ethyl δ-cyclo*Pent-1-*enylvalerate* (IX).—The preceding hydroxy-ester (6·5 g.) in anhydrous ether (60 c.c.) containing pyridine (4·9 g.) was slowly treated with thionyl chloride (3·7 g.) at 0°, and 4 hours later water was added, and the ethereal layer was washed with dilute hydrochloric acid and then with sodium carbonate solution, dried, and distilled. The *ester* (IX) was obtained as a yellow oil (5·0 g.), b. p. 150—160°/5—6 mm., n_D^{15} 1·4572 (Found: C, 73·8; H, 10·7. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%), which may contain some of the corresponding *iso*propyl ester. The free acid (X) obtained by hydrolysis with aqueous alcoholic potassium hydroxide was obtained as a pale yellow oil, b. p. 125—130°/1·6 mm.

*Cyclisation of δ-cyclo*Pentylvaleric *Acid* (X).—(*a*) (cf. Cook and Lawrence, *loc. cit.*). The crude acid (X) (1·5 g.) was converted into the chloride by the action of molecular quantities of thionyl chloride and pyridine in ether at 0°, filtration, and evaporation under diminished pressure. The chloride was treated in carbon disulphide solution with anhydrous stannic chloride in carbon disulphide at −10° and then allowed to reach room temperature overnight. After dilution the organic layer was washed with dilute sodium hydroxide solution and dried, the solvent removed under diminished pressure,

and the residual oil heated with dimethylaniline for 3 hours at 180°. Addition of excess of dilute hydrochloric acid and extraction with ether yielded a brown oil (0·9 g.), which yielded a 2 : 4-*dinitrophenylhydrazone* which, after two crystallisations from ethyl acetate, formed fine, deep-red needles, m. p. 242—243° (Found : C, 58·9; H, 5·7; N, 16·7. $C_{18}H_{18}O_8N_4$ requires C, 58·2; H, 5·5; N, 17·0%). A crystalline oxime could not be obtained.

(*b*) (cf. Bachmann and Dreiding, *loc. cit.*). The crude acid (X) (2·0 g.) was dissolved in a solution of anhydrous zinc chloride (0·3 g.) in acetic acid (7 c.c.) and acetic anhydride (30 c.c.), and after 48 hours the mixture was heated to 70—80° for 1 hour and then well shaken with ether and dilute aqueous sodium hydroxide. The ethereal layer yielded a fraction (0·5 g.), b. p. 100—120°/2 mm., and a higher-boiling residue. The distillate gave a 2 : 4-dinitrophenylhydrazone which after 3 crystallisations from ethyl acetate formed fine, deep-red needles, m. p. 232° [the mixed m. p. with the 2 : 4-dinitrophenylhydrazone prepared by method (*a*) was 232°] (Found : C, 58·9; H, 5·6; N, 17·2%). Again, no crystalline oxime could be obtained.

trans-cyclo*Pentane*-1 : 2-*dicarboxylic Acid*.—Ethyl *cyclo*pent-1-ene-1-carboxylate (67 g.; Cook and Linstead, *loc. cit.*) in ethanol (250 c.c.) was refluxed for 4 hours with aqueous potassium cyanide (34 g. in 70 c.c.), after which aqueous potassium hydroxide (30 g. in 60 c.c.) was added and refluxing continued for a further 6 hours. Concentrated hydrochloric acid (100 c.c.) was then added and *cyclo*pent-1-ene-1-carboxylic acid removed in steam. When kept, the residual solution deposited *trans-cyclo*pentane-1 : 2-dicarboxylic acid which was crystallised from water giving the colourless acid (33 g.), m. p. 160°.

The acid (10 g.) was heated with thionyl chloride (20 c.c.) for 1 hour and then distilled and the di-acid chloride collected as an oil (10·5 g.), b. p. 98—100°/2 mm. This was added with shaking to aqueous ammonia (100 c.c.; *d* 0·88) at 0°. The *diamide* separated from water in highly refracting, rectangular prisms (6·6 g.), m. p. 303° (Found : C, 53·5; H, 7·6; N, 18·0. $C_7H_{14}O_2N_2$ requires C, 53·9; H, 7·7; N, 18·0%).

trans-1 : 2-*Dicyano*cyclo*pentane*.—The preceding diamide (6·6 g.) was refluxed for 2 hours with thionyl chloride (20 c.c.), excess of the reagent removed by distillation, and the residue dissolved in ether, shaken with aqueous sodium carbonate, dried, and distilled. The *dinitrile* (3·6 g.) was collected at 122°/6 mm. as an oil which set to a glassy mass on cooling (Found : C, 69·7; H, 6·9. $C_7H_8N_2$ requires C, 70·0; H, 6·7%).

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THE UNIVERSITY, BRISTOL. [*Received, December* 13*th*, 1949.]

NOTES.

Preparation of N-Bromosuccinimide by an Electrolytic Process. By M. LAMCHEN.

FEW methods for the preparation of *N*-bromosuccinimide have been reported, viz., treatment of succinimide with *N*-bromoacetamide (Seliwanow, *Ber.*, 1893, **26**, 425), or with bromine and sodium hydroxide (Lengfeld and Stieglitz, *Amer. Chem. J.*, 1893, **15**, 215), or quickly brominating an ice-cold alkaline solution of succinimide (Ziegler *et al.*, *Annalen*, 1942, **551**, 80); 75—81% yields are reported in the latter process. *N*-Bromoacetamide used in the first method is obtained (Hofmann, *Ber.*, 1882, **15**, 408) by treating acetamide with bromine and ice-cold sodium hydroxide. All these methods thus employ bromine and sodium hydroxide, the function of which is to produce the hypobromite ion required for the reaction. Half of the bromine used is converted into bromide and is useless for the process; also, at least one equivalent of sodium hydroxide is consumed. In the process described below, hypobromite ions are produced without the use of bromine and with the use of only a small quantity of sodium hydroxide: an ice-cold solution of succinimide and sodium bromide is electrolysed between platinum electrodes with just sufficient sodium hydroxide to keep the solution colourless. Of every two bromide ions discharged at the anode, one again enters the solution as a bromide ion after reaction with hydroxyl ions. Thus, for every bromide ion discharged one molecule of *N*-bromosuccinimide is formed, one hydroxyl ion is produced, and one molecule of hydrogen is liberated. *N*-Bromosuccinimide alone has a low solubility in cold water and separates as a solid on the anode. Every bromide ion is effectively utilised, and the hydroxyl ions required are produced in the process.

The *N*-bromosuccinimide produced varies in colour from straw-yellow to white depending on the conditions used. The crude unwashed product melted at 163°, but by washing it once with a small quantity of ice-cold water the melting point is raised to 178·5°. Yields are 66% for the crude and 54% for the washed product.

The crude product could not be dissolved in benzene but after being washed with water it dissolved quite readily. The same phenomenon was observed with a sample of commercial material. The product is evidently covered with a layer of a benzene-insoluble, water-soluble substance. Ziegler also reported (*Annalen*, 1942, **551**, 80) that benzene was not satisfactory as a solvent for recrystallisation and used water. He considered the covering layer to be succinimide, but from the wash-liquor the present author could recover only *N*-bromosuccinimide. It is believed that the benzene-insoluble substance in this experiment may be sodium succinate because on evaporation of the filtrate at room temperature (or in a vacuum-desiccator) sodium succinate crystallises (its formation is to be expected).

Variation of the current density from 0·03 to 0·3 amp. per square inch made no difference to the

reactions taking place in the process and the same products were obtained in all cases as long as it was low enough to avoid heating of the solution. At higher current densities the product was formed faster and was yellower, but yields were better. If the solution is allowed to become hot the yield drops very rapidly. The use of a rocking anode facilitated the peeling off of the product and gave a slightly better yield and a paler product.

Experimental.—Water was saturated with succinimide and an equimolecular amount of sodium bromide was then dissolved in the solution. This solution was electrolysed between platinum electrodes, at a current density of 0·3 amp. per sq. in., in an ice-bath, and 10% sodium hydroxide solution was added drop by drop till the solution no longer became brown. The anode, if stationary, was shaken at intervals to allow the *N*-bromosuccinimide to drop off; a rocking anode was generally used. When 10 g. of succinimide were used with electrodes 1½ in. square, 3—4 hours sufficed for completion of the reaction. The bulk of the yield was formed during the first hour. 10 G. of crude product, m. p. 163°, were obtained. After filtration, 10 g. of succinimide and 10·3 g. of sodium bromide were dissolved in the filtrate, and the solution was again electrolysed, giving a further yield of 11·85 g. (66%) (m. p. 163°).—UNIVERSITY OF CAPE TOWN, SOUTH AFRICA. [*Received, August 15th*, 1949.]

Preparation of N-Acetyl-N-methylurea by an Electrolytic Process. By M. LAMCHEN.

THE electrolytic method for the preparation of *N*-bromosuccinimide described by the author (preceding note) indicated that imido-hydrogen atoms could be substituted by bromine atoms during electrolysis of an aqueous solution of an imide, sodium bromide, and a small quantity of sodium hydroxide. When the electrolysis is carried out in an ice-cold solution the reaction proceeds only as far as the *N*-bromoimide which, if fairly insoluble in water, is precipitated. This was the case with *N*-bromosuccinimide; when, however, a saturated ice cold solution of acetamide, containing sodium bromide and sufficient sodium hydroxide to keep it colourless, was electrolysed for 10 hours, *N*-bromoacetamide, being soluble, did not crystallise from the solution.

An *N*-bromo-amide would lose hydrogen bromide in warm sodium hydroxide solution, to form the *iso*cyanate (cf. the Hofmann degradation of amides), which would react with suitable compounds. If thus the electrolysed solution of acetamide, sodium bromide, and sodium hydroxide is allowed to become hot, or if the electrolysis is carried out without cooling, the *N*-bromoacetamide, if formed, should lose hydrogen bromide to give methyl isocyanate. In practice white crystals soon appeared and more separated after cooling. These were identified (mixed m. p.) as *N*-acetyl-*N*-methylurea, formed by reaction of the methyl isocyanate with unchanged acetamide.

From a fresh solution 67% yields, calculated on the acetamide, were obtained, but if the filtrate of a previous experiment was used 70—80% yields were obtained. The product is almost pure and is quite white.

Previous methods are those of Young and Clark (*J.*, 1898, **73**, 364; methylamine is treated with acetylurethane) and of Odendal (*Annalen*, 1918, **416**, 228; acetamide is heated with bromine and sodium hydroxide until the solution becomes acid and yellow). Odendal records yields of up to 75%, but the pH is critical and if the solution is slightly too alkaline the yield drops to zero and the process proceeds in a different way. For every molecule of acetamide he used one molecule of sodium hydroxide and more than one molecule of bromine. The electrolytic process described above eliminates the use of bromine and requires only small quantities of sodium hydroxide as the bulk of the required hydroxyl ions are obtained from the electrolysis of the solution; also all the bromide ions should be available for the process and the subsequent splitting off of hydrogen bromide should again regenerate the bromide ions.

Variations of current densities between 0·03 and 0·3 amp. per sq. in. made no difference to the product except that it was formed much faster and yields were better at the higher current densities.

Experimental.—A saturated solution containing acetamide (30 g.) and sodium bromide (15 g.) is electrolysed between platinum electrodes at 0·3 amp. per sq. in. with just sufficient sodium hydroxide (10%) added to prevent the solution becoming brown. Further small quantities of sodium hydroxide may be needed later. Crystals form in the solution after ½—1 hour, depending on the current density. After about 10 hours the solution was cooled and filtered, and the product (20·2 g.) was washed with ice-cold water. After recrystallisation from benzene it had m. p. 180—181° (Found: C, 41·6; H, 6·8. Calc. for $C_3H_5O_2N_2$: C, 41·4; H, 6·9%).—UNIVERSITY OF CAPE TOWN, S. AFRICA. [*Received, August 15th*, 1949.]

The Hydrolysis of NN′-*Dinitro-oxamide*-NN′-*bis*-(2-*ethyl Nitrate*). By J. VAUGHAN.

THE preparation and properties of this dinitrate (III) have been investigated by Wright *et al.* (*e.g.*, Stuart and Wright, *Canadian J. Res.*, 1948, **26**, *B*, 401). The hydrolysis of this compound is of interest because on theoretical grounds it appears that aqueous hydrolysis should proceed quite readily. When the group $-NR'\cdot NO_2$ is linked to an alkyl group R, as in (I), the new R–N linkage should be relatively

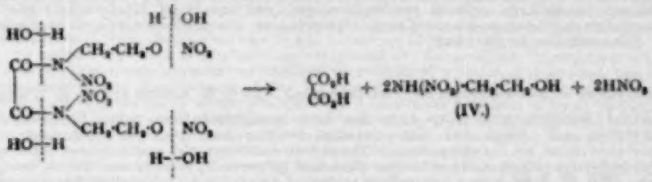
(I.) (II.) (III.)

stable because the electrophilic tendency of the amino-nitrogen atom can be partly met by the electron-donating effect (*a*) of the alkyl group. When the group $-NR'\cdot NO_2$ is linked to a carbonyl group, as in (II), the electrophilic tendency of the amino-nitrogen atom and the electromeric effect (*b*), caused by the

strong displacement towards the carbonyl oxygen, combine to make the carbonyl carbon susceptible to nucleophilic attack. The carbonyl–N linkage in (II) should thus be relatively unstable to hydrolysis. This argument is supported by the fact that ethylenedinitroamine, a compound of type (I), is very much more stable to hydrolysis than nitrourea, a compound of type (II). Ethylenedinitroamine may be prepared by the action of boiling water on dinitroethyleneurea (Franchimont and Klobbie, *Rec. Trav. chim.*, 1888, **7**, 17), but nitrourea is readily decomposed by hot water and the decomposition is accelerated by the presence of bases (Sidgwick's "Organic Chemistry of Nitrogen," 1937, p. 280). Compound (III), like nitrourea, should be fairly readily attacked by warm water, but the possibility of the alkyl nitrate groupings also undergoing hydrolysis is to be borne in mind.

Preliminary experiments on the hydrolysis of (III), which is insoluble in water, have been carried out at 49° with a stationary amide–water interface. The results can be summarised as follows: (i) the acidity developed is, approximately, accounted for by the oxalic and nitric acids formed; (ii) within the limits of experimental error the *molar* ratio of nitric to oxalic acid formed is 2 : 1.

On the basis of these preliminary results, therefore, the hydrolysis of the substituted oxamide can be represented thus



(IV.)

Monoethanolnitroamine (nitro-2-hydroxyethylamine) (IV) contains an acidic hydrogen atom; it might be expected, therefore, that this would be estimated in the total acidity. However, in the presence of acids, this compound is readily decomposed into ethylene glycol and nitrous oxide (Franchimont, *Rec. Trav. chim.*, 1902, **21**, 50). It was established during the present work that nitrous oxide was formed during the hydrolysis in amount corresponding to at least two-thirds of the theoretical.

Experimental.—Hydrolysis was followed by determination of the loss in weight of the amide and estimation of hydrolysis products. The substituted oxamide was recrystallised from acetone, dried *in vacuo* over phosphoric oxide, and passed through a 100-mesh B.S. sieve. Portions (0·5 g.) were each placed in contact with distilled water (40 ml.) in 100-ml. conical Pyrex flasks fitted with standard ground-glass stoppers. 0·01 G. of lauryl alcohol was also added in each case in order to get thorough wetting of the crystals, and the flasks were then placed in a thermostat at 49°. Although the lauryl alcohol would probably increase the rate of hydrolysis, it was considered unlikely that the course of hydrolysis would be affected. In this way an approximately constant initial area of interface between amide and water could be assumed.

Flasks were removed at intervals, and the solid residue filtered off. This was dried and weighed, and the m. p. of each precipitate indicated that pure (III) had been recovered. The filtrates in each case gave positive tests for the presence of oxalic and nitric acids. The complete filtrate then underwent the following sequence of determinations: (i) of total acidity by titration, (ii) of oxalic acid as calcium oxalate by permanganate, (iii) of nitric acid by "nitron." In no case could more than a trace of nitrous acid be detected in the filtrate, using the Griess–Ilosvay reagent. The results are summarised in the table.

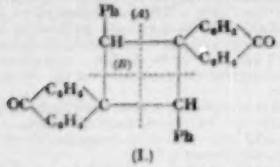
Time (days) at 49°.	Wt. of compound taken (g.).	% not hydrolysed.	Total acidity (ml., *N*/10).	Nitric acid (ml., *N*/10).	Oxalic acid (ml., *N*/10).
4	0·4995	not determined	17·4	9·1	9·4
8	0·5002	51·9	29·3	16·8	15·1
12	0·5000	26·9	40·7	19·6	19·5
17	0·5087	20·4	46·8	22·6	24·9
25	0·5021	14·3	48·6	24·4	25·1

The author thanks the Chief Scientist of the Ministry of Supply for permission to publish this work, which was carried out in the Armament Research Department of the Ministry in 1945.—CANTERBURY UNIVERSITY COLLEGE, CHRISTCHURCH, NEW ZEALAND. [*Received, September 29th*, 1949.]

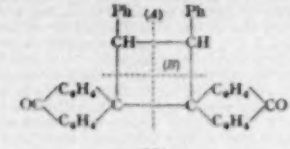
Reactions in Sunlight. By FAWZY GHALI BADDAR.

MUSTAFA and ISLAM (*J.*, 1949, S 81) claimed that the dimer obtained by exposing 9-benzylideneanthrone in benzene solution to sunlight has the structure (II) because (i) it lacks colour, (ii) on being heated at 270° it regenerates the monomer, and (iii) it has the correct molecular weight. The product may equally, however, have the isomeric structure (I), which would give only 9-benzylideneanthrone on thermal decomposition, whether cleavage of the bonds occurs along (*A*) or along (*B*); if it has the isomeric structure (II), thermal decomposition would give rise to a mixture of the monomer, stilbene, and dianthraquinonyl. Stobbe and Bremer (*J. pr. Chem.*, 1929, **123**, 1) isolated two dimers of benzylideneacetophenone; that which gave stilbene on thermal decomposition was given a structure analogous to (II), whereas that which gave mainly the monomer was assigned a structure analogous to (I). The fact

that the above authors failed to isolate any stilbene among the decomposition products supports structure (I) rather than (II).



(I.)



(II.)

Similarly, in the photo-reactions between retenequinone and 9-benzylidenexanthen or methyleneanthrone and between chrysenequinone and triphenylethylene (Mustafa, *J.*, 1949, S 83), the constituent molecules can theoretically unite in two ways to give two isomerides, which would give identical products on thermal decomposition.—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, ABBASSIA, CAIRO, EGYPT. [*Received, October 5th*, 1949.]

3-*Hydroxy*-4 : 5-*dimethoxybenzoic Acid Derivatives*. By J. R. ANSTER and D. E. WHITE.

3-HYDROXY-4 : 5-DIMETHOXYBENZOIC ACID has been synthesised from gallic, 5-nitroveratric, and 5-bromoveratric acid. Späth and Röder's method starting from gallic acid (*Monatsh.*, 1922, **43**, 93) is most convenient for the preparation of the acid in quantity; the acid has been characterised by the acetyl derivative, which melts 10° higher than that prepared by Shriner and McCutchan (*J. Amer. Chem. Soc.*, 1929, **51**, 2193) from a low-melting sample of 3-hydroxy-4 : 5-dimethoxybenzoic acid.

Ethylation with ethyl sulphate and alkali gave **3** : 4-dimethoxy-5-ethoxybenzoic acid, m. p. 117—118°. Seshadri and Venkateswarlu (*Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 296) describe this acid as melting at 164°, only 3° lower than their sample of trimethylgallic acid. This m. p. appears to be in error as the isomeric **3** : 5-dimethoxy-4-ethoxybenzoic acid (Bogert and Ehrlich, *J. Amer. Chem. Soc.*, 1919, **41**, 801) melts more than 40° lower than trimethylgallic acid.

Methyl and *ethyl* **3** : 4-*dimethoxy-5-ethoxybenzoate* were prepared with the appropriate alcohol and sulphuric acid.

Experimental (M. p.s are corr.).—**3**-*Hydroxy*-4 : 5-*dimethoxybenzoic acid*. Prepared by the method of Späth and Röder (*loc. cit.*), this acid formed colourless needles (from water), m. p. 195—196°, considerably depressed by admixture of syringic acid (m. p. 207°). When refluxed (1 g.) with acetic anhydride (5 ml.) and pyridine (1 drop) for 30 minutes, it gave an acetyl derivative (1 g.), isolated by pouring the mixture into water and forming long colourless prisms (from aqueous methyl alcohol), m. p. 148° (Found : C, 55·05; H, 5·2. Calc. for $C_{11}H_{12}O_6$: C, 55·0; H, 5·0%), considerably depressed by admixture with acetylsyringic acid (m. p. 184—186°).

3 : 4-*Dimethoxy-5-ethoxybenzoic acid*. The above acid (18 g.) in 10% sodium hydroxide solution (80 ml.) was boiled under reflux during the addition, during 30 minutes, of ethyl sulphate (40 ml.) and 10% sodium hydroxide solution (132 ml.). Refluxing was continued for 1 hour, and ethyl sulphate (20 ml.) and 20% sodium hydroxide solution (40 ml.) added during the next 15 minutes. After refluxing for a further 30 minutes, ethanol (17 ml.) was removed by distillation, and the solution treated with charcoal, cooled, and acidified with hydrochloric acid. The acid (20 g.) formed colourless needles and plates from 10% alcohol (8·0 ml.) and after two crystallisations melted constantly at 117—118° (15 g.) (Found : C, 58·5; H, 6·35. Calc. for $C_{11}H_{14}O_6$: C, 58·4; H, 6·2%).

Methyl and ethyl esters. A solution of **3** : 4-dimethoxy-5-ethoxybenzoic acid (5 g.) in the appropriate alcohol (30 ml.) was refluxed with sulphuric acid (0·2 ml.) for 8 hours and the ester isolated by distillation of the alcohol, dissolution of the residue in ether, and washing of the extract to remove acids. After drying (Na_2SO_4) and distillation of the ether the ester remained. The *methyl* ester crystallised as colourless needles, m. p. 51·5° (2·5 g.) (Found : C, 60·09; H, 6·76. $C_{12}H_{16}O_6$ requires C, 59·98; H, 6·71%), from 40% methyl alcohol. The *ethyl* ester was a colourless oil, b. p. 139—140°/3 mm., 105—106°/0·1 mm., n_D^{25} 1·5268, n_D^{20} 1·5160 (2·2 g.) (Found : C, 61·5; H, 7·4. $C_{13}H_{18}O_6$ requires C, 61·3; H, 7·1%).

The authors acknowledge financial support from the Commonwealth Research Grant to Australian Universities and microanalyses by Drs. Weiler and Strauss.—UNIVERSITY OF WESTERN AUSTRALIA. [*Received, October 24th*, 1949.]

Certain Substituted Benzaldehydes and Substituted Benzaldehyde Dinitrophenylhydrazones.
By J. B. BOWEN and E. M. WILKINSON.

DURING investigations on the adsorption of 2 : 4-dinitrophenylhydrazones on activated alumina, a series of substituted benzaldehyde 2 : 4-dinitrophenylhydrazones was prepared. Nine of these derivatives are new and it therefore seemed desirable to record the new data. The Stephen reduction of nitriles (*J.*, 1925, **127**, 1874) has been applied for the first time to the synthesis of four of the aldehydes used. These preparations are briefly recorded.

m-Tolualdehyde.—*m*-Tolunitrile (8·7 g.) was added to anhydrous stannous chloride (25 g.) dissolved in dry ether (50 c.c.) saturated with dry hydrogen chloride. After 2 days the crystals which had deposited were filtered off and steam-distilled. The aldehyde was ether-extracted from the distillate, dried, and distilled in an atmosphere of carbon dioxide. B. p. 198°/756 mm. Yield, 50%. Von Auwers (*Annalen*, 1915, **408**, 237) gives b. p. 195°/745 mm.

m-Chlorobenzaldehyde.—*m*-Chlorobenzonitrile (2·9 g.) and stannous chloride (10 g.) in dry ethereal hydrogen chloride (30 c.c.) gave similarly, after 24 hours, the aldehyde of b. p. 213—214° (53%). Erdmann and Schwechten (*ibid.*, 1890, **260**, 59) give b. p. 213—214°.

p-Bromobenzaldehyde.—*p*-Bromobenzonitrile (10 g.) and stannous chloride (21 g.) in dry ethereal hydrogen chloride (300 c.c.), when kept overnight, gave an aldehyde which, when similarly isolated and then recrystallised from dilute methanol, had m. p. 57° (62%). Adams and Vollweiler (*J. Amer. Chem. Soc.*, 1918, **40**, 1738) give m. p. 56—57°.

p-Iodobenzaldehyde.—*p*-Iodobenzonitrile (10 g.) in dry ether (50 c.c.) with saturated, dry, ethereal hydrogen chloride solution (150 c.c.) containing anhydrous stannous chloride (40 g.) gave similarly, after 24 hours, the aldehyde (56%), m. p. 77° (from aqueous ethanol). Willgerodt and Bogel (*Ber.*, 1905, **38**, 3451) give m. p. 78°.

In some cases more crystals of the aldimine stannichloride were deposited in the reaction flask on further storage, so that the yields could be improved a little if necessary.

The Sandmeyer procedure described by Clark and Read (*Org. Synth.*, Coll. Vol. I, p. 514) for the preparation of *o*- and *p*-tolunitrile was applied to obtain the necessary *m*-tolunitrile, *m*-chloro-, *p*-bromo-, and *p*-iodo-benzonitrile in 53, 59, 67, and 68% yield, respectively, from the appropriate amines.

Preparation of the Dinitrophenylhydrazones.—Except where otherwise stated, the general procedure for the preparation of these derivatives was to add a solution of the aldehyde in methanol to a slight excess of the reagent dissolved in sulphuric acid–methanol (1 : 10) or dilute hydrochloric acid. The derivatives so obtained were repeatedly recrystallised to constant m. p. using, in most cases, two different solvents in succession, and dried *in vacuo* at 100° for analysis. The *m*-amino-compound is an exception in this respect, in that we failed to recrystallise it in a satisfactory manner without decomposition. The solubilities in benzene at room temperature were determined by using a Spekker photoelectric absorptiometer to measure concentrations. The tungsten lamp in conjunction with the usual heat filters and "Ilford 601" violet filters were suitable for all the solutions examined.

M. p.s were determined by using short-range Anschütz-type thermometers and are corrected except where otherwise specified.

m-Aminobenzaldehyde 2 : 4-*dinitrophenylhydrazone.* *m*-Aminobenzaldehyde was prepared *in situ* by Buck and Ide's method (*Org. Synth.*, Coll. Vol. II, p. 130), and its solution in aqueous hydrochloric acid added directly to a saturated solution of the reagent in the same medium. The brownish-red precipitate of the *dinitrophenylhydrazone* was washed with distilled water until free from chloride ions and dried in a vacuum desiccator. Solubility in benzene, 13 mg./100 ml. It decomposes from about 220° (Found : N, 23·0. $C_{13}H_{11}O_4N_5$ requires N, 23·3%).

p-Aminobenzaldehyde 2 : 4-*dinitrophenylhydrazone.* *p*-Aminobenzaldehyde, prepared *in situ* from *p*-nitrotoluene by Beard and Hodgson's method (*J.*, 1944, 4), was used immediately in dilute acid solution as described for *m*-aminobenzaldehyde. The precipitated *dinitrophenylhydrazone* was thoroughly washed until free from mineral acid and was obtained as a light-brown powder, m. p. 192·5—194·5° (slight decomp.), after recrystallisation from methanol (Found : N, 23·4. $C_{13}H_{11}O_4N_5$ requires N, 23·3%).

m-, bright yellowish-orange crystals (from aqueous pyridine and then from xylene) (solubility in benzene, 34 mg./100 ml.), m. p. 256—257° (Found : N, 15·2. $C_{13}H_9O_4N_4Br$ requires N, 15·3%), and *p-bromobenzaldehyde* 2 : 4-*dinitrophenylhydrazone*, bright orange crystals (from aqueous pyridine and then from xylene) (solubility in benzene, 25 mg./100 ml.), m. p. 256—257·5° (Found : N, 15·5%), were obtained by the general method.

p-Carboxybenzaldehyde 2 : 4-*dinitrophenylhydrazone* was prepared by adding the reagent in hot dilute hydrochloric acid to the aldehyde in the same solvent. The precipitated derivative was filtered hot and obtained as bright light-orange crystals from aqueous pyridine. It was further recrystallised from nitrobenzene. It was practically insoluble in benzene. M. p. 319·5—320·5° (uncorr.) (Found : N, 17·1. $C_{14}H_{10}O_6N_4$ requires N, 17·0%).

p-Iodobenzaldehyde 2 : 4-*dinitrophenylhydrazone* was obtained by the general method. The precipitated derivative was washed with boiling dilute hydrochloric acid and then with water. After recrystallisation from an aqueous pyridine–methanol and finally from xylene it yielded pale orange-brown crystals (solubility in benzene, 38 mg./100 ml.), m. p. 256·5—257·5° (Found : N, 13·7. $C_{13}H_9O_4N_4I$ requires N, 13·6%).

The standard method yielded 2 : 4-*dinitrophenylhydrazones* from *p*-carbomethoxybenzaldehyde, pale-orange, m. p. 263·5—265° (from aqueous pyridine) (Found : N, 16·4. $C_{15}H_{12}O_6N_4$ requires N, 16·2%) (solubility in benzene, 14 mg./100 ml.), *m*-methoxybenzaldehyde, brilliant red crystals (from pyridine and then from xylene) (solubility in benzene, 32·5 mg./100 ml.), m. p. 218·5—219·5° (Found : N, 17·7. $C_{14}H_{12}O_5N_4$ requires N, 17·7%), and *m*-tolualdehyde, bright orange-red crystals (from aqueous pyridine and then from xylene) (solubility in benzene, 152 mg./100 ml.), m. p. 211·5—212·5° (Found : N, 18·8. $C_{14}H_{12}O_4N_4$ requires N, 18·7%).

One of us (J. B. B.) gratefully acknowledges his indebtedness to the Chemical Society for a research grant and the other (E. M. W.) to the Department of Scientific and Industrial Research for a maintenance grant.—The Edward Davies Chemical Laboratories, University College of Wales, Aberystwyth. [*Received, October 31st*, 1949.]

The Resolution of p-Chlorobenzhydrol. By G. H. Green and J. Kenyon.

The main object in resolving *p*-chlorobenzhydrol into its optical isomerides was to compare the readiness with which alkyl–oxygen fission occurred during reactions of this compound and its derivatives with that of *o*-chlorobenzhydrol and its corresponding derivatives. The latter compounds were shown (Balfe *et al.*, *J.*, 1946, 797) to exhibit only negligible alkyl–oxygen fission due, doubtless, to the deactivating influence of the chlorine substituent. For this reason and also because it was found that *p*-chlorobenz-

hydryl hydrogen phthalate undergoes hydrolysis to the carbinol with extreme readiness further investigation of the reactions of *p*-chlorobenzhydrol and its derivatives was not proceeded with.

Experimental.—*p*-Chlorobenzhydrol was readily obtained in good yield by the reduction of *p*-chlorobenzophenone with either aluminium isopropoxide or, very conveniently, with zinc dust (an equal weight) and alcoholic sodium hydroxide (10 vols.; 10%). It separated from light petroleum in needles, m. p. 58·5—59·5°.

(±)-*p-Chlorobenzhydryl hydrogen phthalate*. A solution of phthalic anhydride (15 g.) in boiling anhydrous pyridine (10 g.) was rapidly cooled to about 50° and mixed with *p*-chlorobenzhydrol (20 g.), and the whole mass thoroughly stirred; it gradually stiffened and set solid within a few hours. It was then heated at 60° for 2 hours, cooled, and dissolved in acetone and the solution poured, with stirring, into water containing a slight excess of hydrochloric acid. The resulting solid was dissolved in ether, extracted therefrom with sodium carbonate (5%), and finally precipitated with cold dilute hydrochloric acid. (±)-p-*Chlorobenzhydryl hydrogen phthalate* separated from benzene in needles, m. p. 152° [Found (by titration in acetone–ethanolic solution with N/10-NaOH): *M*, 366·8. $C_{21}H_{15}O_4Cl$ requires *M*, 366·8].

(−)-*p-Chlorobenzhydryl hydrogen phthalate*. The only reasonably successful procedure for obtaining this compound appears to be to leave a solution of the brucine salt of the (±)-ester in ethyl acetate to evaporate at room temperature until a suitable amount of crystallisation has occurred.

A solution of the (±)-hydrogen phthalate (55 g.) and brucine (59·4 g.) in dry ethyl acetate (275 c.c.) was divided between eleven conical flasks (100 c.c.), each containing a "seed" of brucine salt, and left uncovered during 4 days. The various crystalline crops, m. p. 113° (decomp.), were separated by decantation of the mother liquors and each recrystallised twice more by the same procedure. Further recrystallisation was precluded owing to progressive decomposition of the salt, presumably by hydrolysis, into *p*-chlorobenzhydrol and brucine hydrogen phthalate. The recrystallised brucine salt was dissolved in acetone and decomposed with cold dilute hydrochloric acid, and the liberated acid ester purified by solution in sodium carbonate as described above (yield, 9 g.; m. p. 135°). It suffered no change either in m. p. or rotatory power by crystallisation from benzene.

(+)-*p-Chlorobenzhydryl hydrogen phthalate*. The combined mother liquors from the first crystallisation of the brucine salt on storage deposited two further small crops of salt which were removed by filtration. This final filtrate on decomposition yielded the (+)-acid ester (15 g.), m. p. 140°, $[\alpha]_{5461}$ +1·1° (*l*, 1·0; *c*, 26·7 in acetone solution).

(−)-*p-Chlorobenzhydrol*. The (−)-acid phthalic ester (5 g.) in hot methanol (50 c.c.) was mixed with sodium hydroxide solution (5 c.c.; 40%) and the whole heated on the steam-bath for 10 minutes. Water (200 c.c.) was added to the cooled solution to dissolve the precipitated sodium hydrogen phthalate, and the liberated carbinol was extracted with ether. It (3 g.) had m. p. 54—56°, unchanged by crystallisation from light petroleum.

(+)-*p-Chlorobenzhydrol*. The (+)-acid ester (7 g.) by similar treatment yielded (+)-*p*-chlorobenzhydrol (4 g.), m. p. 50—54°.

Specific rotatory powers (*l*, 1·0; temp. 20°).

Solvent.	*c*, g./100 c.c. of solution.	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.	Solvent.	*c*, g./100 c.c. of solution.	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.
(−)-*p*-Chlorobenzhydryl hydrogen phthalate.					(+)-*p*-Chlorobenzhydrol.				
Chloroform ...	13·3	−3·5°	−3·7°	−4·9°	Chloroform	20·0	+13·7	+14·1	+15·5
Acetone	13·3	3·8	4·2	4·2					
					(−)-*p*-Chlorobenzhydrol.				
Acetone	13·3	18·7	20·4	21·7	Chloroform	6·7	32·1	34·1	36·0
Ethanol (99%)	6·7	18·9	20·3	22·2	Benzene ...	6·7	29·9	31·5	34·6
Ethyl acetate	6·7	23·4	24·3	27·6					

We have pleasure in expressing our thanks to Imperial Chemical Industries Ltd. for a grant.—Battersea Polytechnic, London, S.W.11. [*Received, November* 4th, 1949.]

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p-*Bishalogenoacetylbenzenes*. By W. C. J. Ross.

During the examination of possible cytotoxic substances containing two or more groupings capable of reacting with functional centres in biological systems (Everett and Ross, *J.*, 1949, 1972; Goldacre, Loveless, and Ross, *Nature*, 1949, **163**, 667) the preparation of *p*-bishalogenoacetylbenzenes was undertaken. These compounds had previously been prepared by Ruggli and Gassenmeier (*Helv. Chim. Acta*, 1939, **22**, 496) by direct halogenation of *p*-diacetylbenzene which was obtained by the sequence of reactions: *p*-xylene ⟶ terephthalic acid ⟶ terephthaloyl chloride ⟶ terephthalyldiacetoacetic ester ⟶ diacetylbenzene. The required compounds can be prepared more directly by the following route: terephthaloyl chloride ⟶ *p*-bisdiazoacetylbenzene ⟶ bishalogenoacetylbenzene.

p-*Bisdiazoacetylbenzene*. Terephthalic acid (3 g.), thionyl chloride (10 ml.), and pyridine (1 drop) were heated on a steam-bath for 3 hours. Dry benzene (30 ml.) was added, and the mixture was evaporated under reduced pressure. The chloride (2 g.), m. p. 82—84°, crystallised from light petroleum (b. p. 60—80°). Terephthaloyl chloride (1·5 g.) dissolved in dry ether (50 ml.) was gradually added to an ice-cooled ethereal (200 ml.) solution of diazomethane [from nitrosomethylurea (5 g.)]. Next day, the dense yellow precipitate (2 g.) was collected and recrystallised from benzene. It formed short needles, decomp. >370° when slowly heated but melting with decomp. when placed in a bath at 200°

(Found: C, 56·4; H, 3·2. $C_{16}H_4O_2N_4$ requires C, 56·1; H, 2·8%. The *diazo*-compound is difficult to analyse since it explodes on heating).

p-Bishalogenoacetylbenzenes. (*a*) The diazo-ketone (1 g.) was suspended in ether (50 ml.) and treated with concentrated hydrochloric acid (0·5 ml.). After the evolution of nitrogen had subsided the chloroacetyl compound separated. It formed needles, m. p. 186°, from methanol (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 153°) (Found: C, 52·0; H, 3·6. Calc. for $C_{10}H_6O_2Cl_2$: C, 52·0; H, 3·5%). (*b*) *p*-Bisbromoacetylbenzene, prepared similarly, formed prismatic needles, m. p. 176—177°, from methanol (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 173°). (*c*) The bromo-ketone (500 mg.) and sodium iodide (500 mg.) in acetone (10 ml.) were warmed on a steam-bath for 10 minutes. The iodo-compound which separated on adding water gave needles, m. p. 135°, from aqueous methanol (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 135°).

This investigation was carried out during the tenure of a Sir Halley Stewart Fellowship.—THE CHESTER BEATTY RESEARCH INSTITUTE, FULHAM ROAD, LONDON, S.W.3. [*Received, December 1st,* 1949.]

Acetylene and Acetylenic Compounds in Organic Synthesis.

THE TILDEN LECTURE, DELIVERED BEFORE THE SOCIETY AT THE IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, ON OCTOBER 20TH, 1949.

By E. R. H. JONES, D.Sc., F.R.I.C.

RECENT developments in acetylene chemistry have been many and varied and, as a result, the opportunities for the use of acetylene and acetylenic compounds in synthetic work have been greatly extended. The advantages to be gained by employing these versatile and reactive compounds are not too widely appreciated and consequently when this lecture was first planned, more than two years ago, it had been intended to attempt a broad review of the whole field. In the meantime, however, several aspects of the subject have been admirably dealt with (Johnson, "Some Applications of Acetylenic Compounds in Organic Synthesis," R.I.C., 1948; Bergmann, "Acetylene Chemistry," 1948; Sir Ian Heilbron, Pedler Lecture, *J.*, 1948, 386; Reppe, *Experientia*, 1949, **5**, 93), and this lecture is therefore somewhat more restricted in its scope than would otherwise have been the case. Even with this almost welcome limitation the selection of topics has been by no means easy and to a large extent the examples chosen to illustrate the general theme have been taken from recent work in the laboratories at Imperial College, London, and at Manchester University.

Although the original discovery of acetylene was made by Davy more than a hundred years ago, and many of its reactions and those of simple acetylenic compounds were investigated from 1860 onwards, especially by Berthelot and his school, it was not until the turn of the century that acetylene became readily available with the introduction of a method for the manufacture of calcium carbide. In the first instance, this availability of carbide led to the widespread use of acetylene as an illuminant (1894), to the utilisation of the cyanamide process for nitrogen fixation (1904), and to the employment of the oxy-acetylene flame (1906). The potentialities for organic syntheses, realised by Berthelot as early as 1872, were to remain largely unexploited for many years. It was not until World War I that the conversion of acetylene into acetaldehyde, long studied in the laboratory, was realised commercially, and during World War II many processes based on acetylene, but not competitive under normal conditions, were operated on a large scale in Germany. The remarkable work of Reppe and his collaborators, revealing so many novel and fascinating reactions in the field of acetylene chemistry emanated largely from the need for the utilisation of acetylene as a major starting material for the German organic chemical industry.

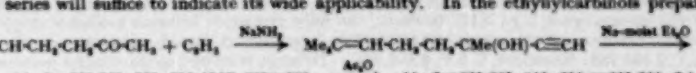
At just about the time when carbide became readily available, Nef (*Annalen*, 1899, **308**, 264) discovered a reaction which, probably more than any other, has fostered the employment of acetylenic compounds in synthetic work. Reasoning from analogy with the zinc alkyls he demonstrated that the sodium derivative of phenylacetylene could be condensed with carbonyl compounds to give acetylenic carbinols (*e.g.*, I), previously available only from the corresponding

$$\mathrm{Ph{\cdot}C{\equiv}CNa + \overset{\overset{\mathrm{CH_3}}{|}}{C}O{\cdot}Ph \longrightarrow Ph{\cdot}C{\equiv}C{\cdot}\overset{\overset{\mathrm{CH_3}}{|}}{C}(OH){\cdot}Ph \quad (I.)}$$

ethylenic carbinols by halogenation and dehydrohalogenation procedures. The Grignard reagents, discovered shortly afterwards, proved to be useful in this connection and in the succeeding fifty years this reaction has been found to be of an extremely general character, occurring between any compound containing a free ethynyl group and a carbonyl compound in the presence of a suitable condensing agent (cf. Johnson, "Acetylenic Compounds," Vol. I). The scope of this addition reaction, especially for large-scale applications, has been greatly extended by the efforts of Reppe and his collaborators, who have developed the use of copper and related acetylides as catalysts. This discovery was applied most successfully to the manufacture of butynediol ($HO{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH$) by the condensation of acetylene with formaldehyde, the first stage in the Reppe process for the production of butadiene.

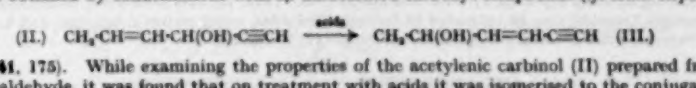
One of the best-known synthetic uses of the ethynylcarbinols arises from their partial hydrogenation, followed by anionotropic rearrangement of the vinylcarbinols to the isomeric primary alcohols or their derivatives. The value of this reaction was early appreciated in the terpene series as is illustrated by the syntheses of linaloöl (Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 182), of farnesol and nerolidol (Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 492), and of phytol (Fischer and Löwenberg, *Annalen*, 1929, **475**, 183). Many more examples of the

application of this convenient procedure are on record but some further instances from the steroid series will suffice to indicate its wide applicability. In the ethynylcarbinols prepared

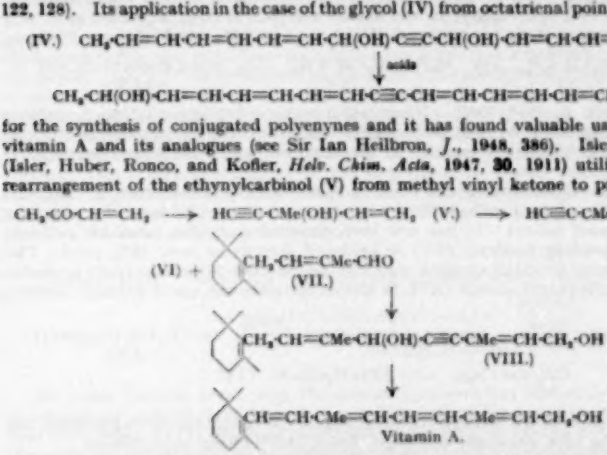


from the 17-ketones of the steroid series the hydroxyl group has an orientation (β) different from that of the 17-hydroxylated substances isolated from the adrenal cortex. After partial hydrogenation and rearrangement to the primary alcohol, however, a hydroxyl group with the correct orientation (α) can be introduced by hydroxylation with osmium tetroxide [*cf.* the synthesis of 17-hydroxyprogesterone (Prins and Reichstein, *Helv. Chim. Acta*, **1941**, **24**, 945) and the synthesis of Kendall's Compound *E* (Sarett, *J. Biol. Chem.*, **1946**, **162**, 601)].

A major extension of the field of application of acetylenic carbinols in organic synthesis arose from the discovery of the ready anionotropic rearrangement undergone by the carbinols and glycols obtained by condensations with αβ-unsaturated carbonyl compounds (*cf. Ann. Reports*, **1944**, **41**, 175). While examining the properties of the acetylenic carbinol (II) prepared from crotonaldehyde, it was found that on treatment with acids it was isomerised to the conjugated vinylacetylenic alcohol (III). The broad scope of this reaction has been clearly demonstrated, its kinetics have been studied, and the marked influence of substituent groups, which produce variations in rates of isomerisation of 10^9, is a notable feature (Braude and Jones, *J.*, **1944**, 436; **1946**, 122, 128). Its application in the case of the glycol (IV) from octatrienal points to its potentialities



for the synthesis of conjugated polyenynes and it has found valuable use in the synthesis of vitamin A and its analogues (see Sir Ian Heilbron, *J.*, **1948**, 386). Isler and his co-workers (Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, **1947**, **30**, 1911) utilised the anionotropic rearrangement of the ethynylcarbinol (V) from methyl vinyl ketone to prepare the C_{15} alcohol



(VI) which, by condensation with the C_{14} aldehyde (VII), furnished the glycol (VIII), ultimately converted into vitamin A.

The vinylcarbinols obtained by partial hydrogenation of the ethynyl compounds rearrange

even more readily and in the simple case of the carbinol (IX) derived from crotonaldehyde it was shown that isomerisation occurred to give the secondary butadienylcarbinol (X) (Jones, Heilbron, McCombie, and Weedon, *J.*, **1945**, 84). It appears from recent work (Nazarov and Fisher, *Chem. Abstracts*, **1949**, **43**, 112) that the rapid isomerisation to the conjugated secondary carbinol is succeeded by a slow conversion into the primary sorbyl alcohol (XI).

As has already been indicated, a considerable variety of procedures can be utilised for the preparation of the normal acetylenic carbinols, *i.e.*, the αβ-acetylenic carbinols [>C(OH)·C≡C·]. For the βγ-analogues (*e.g.*, XII), however, the only procedure hitherto available employs the reaction between ethylene oxides and sodium acetylide in liquid ammonia (*cf.* Kreimeier, U.S.P. 2,106,182; Macallum, U.S.P. 2,125,284). Its scope is limited by the relative inaccessibility of the oxides and by the poor yields obtained. Even with ethylene oxide it is not easy to achieve yields of more than 50% and with increasing substitution the yields fall appreciably (propylene

$$CH_2(O)CH{-}CH_3 + NaC{\equiv}CH \longrightarrow HO{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH \quad (XII.)$$

oxide gives about 35% and *iso*butylene oxide only about 20% yields; Haynes and Jones, unpublished). It may be noted that it was while searching for new methods of effecting the condensation between ethylene oxide and acetylene, that the remarkable polymerisation of acetylene to *cyclo*octatetraene was revealed (Reppe, Schichting, Klager, and Topel, *Annalen*, **1948**, **560**, 1). Seeking a more convenient route to the βγ-acetylenic alcohols it has now been established (Henbest, Jones, and Walls, *J.*, **1949**, 2696) that the Reformatsky type of condensation, initially reported by Zeile and Meyer (*Ber.*, **1942**, **75**, 356) between *cyclo*hexanone and propargyl bromide, can be extended to include aldehydes, unsaturated aldehydes, and ketones, in reactions with a variety of substituted propargyl bromides.

$$>C{=}O + BrCH_2{\cdot}C{\equiv}CH \xrightarrow{Zn} >C(OH){\cdot}CH_2{\cdot}C{\equiv}CH$$

On the basis of our present knowledge it is hardly to be expected that any widely applicable methods can be devised for the preparation of γδ-acetylenic alcohols. However, two novel examples of the formation of these rather inaccessible alcohols have recently been discovered. The condensation between epichlorohydrin and sodium acetylide in liquid ammonia gave, very unexpectedly, the primary alcohol, pentenynol (XIII) in about 40% yield (Haynes, Heilbron, Jones, and Sondheimer, *J.*, **1947**, 1583). Unequivocal evidence indicates that the initial step in this reaction is substitution to yield the acetylenic oxide followed by rearrangement to the alcohol, rather than the alternative addition to the oxide ring and subsequent elimination of sodium chloride.

$$HC{\equiv}CNa + Cl{\cdot}CH_2{\cdot}CH(O)CH_2 \longrightarrow [HC{\equiv}C{\cdot}CH_2{\cdot}CH(O)CH_2] \longrightarrow \underset{(XIII.)}{HC{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH}$$

The other example originated from the work of Paul (*Bull. Soc. chim.*, **1935**, **2**, 745), who described the formation of the pentenol (XIV) from tetrahydrofurfuryl chloride by treatment with sodium in an inert solvent. It has now been observed that with sodamide in liquid ammonia the corresponding pentynol (XV) is produced directly in over 70% yield. This pentynol, which has many potential synthetic uses, thus becomes one of the most easily accessible acetylenic alcohols. Propargyl alcohol (XVI) is almost certainly the major product resulting

$$\underset{(XIV.)}{HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH_2} \longleftarrow CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}\underset{\displaystyle O}{CH}{\cdot}CH_2Cl \xrightarrow{NaNH_2} \underset{(XV.)}{HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH}$$

$$CH_2(O)CH{\cdot}CH_2Cl \longrightarrow HO{\cdot}CH_2{\cdot}C{\equiv}CH \quad (XVI.)$$

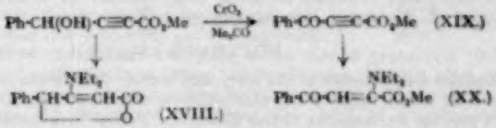
from the similar treatment of epichlorohydrin but the optimum conditions for its formation and isolation have yet to be fully elucidated (Eglinton, Jones, and Whiting, unpublished).

The experiences of earlier workers on the carboxylation of ethynylcarbinols were not encouraging, but it was found that by careful attention to the reaction conditions, especially to the choice of solvent for the Grignard complex, excellent conversions into the hydroxy-acetylenic

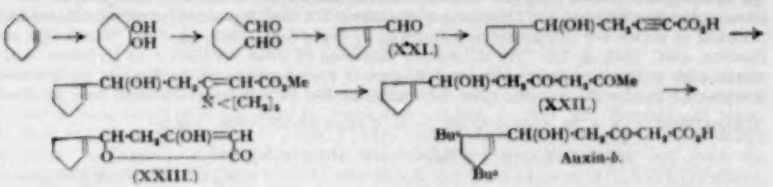
$$>C(OH){\cdot}C{\equiv}CH \xrightarrow{EtMgBr} >C(O{\cdot}MgBr){\cdot}C{\equiv}CMgBr \xrightarrow[H_2O]{CO_2} \underset{(XVII.)}{>C(OH){\cdot}C{\equiv}C{\cdot}CO_2H}$$

acids (XVII) could be obtained (Haynes and Jones, *J.*, 1946, 503). These acids have already found several synthetical applications, for example, by partial hydrogenation, syntheses of αβ-ethylenic lactones are possible (Haynes and Jones, *J.*, **1946**, 954). With nucleophilic reagents, addition reactions of the esters lead to β-substituted γ-hydroxyacrylic esters which are spontaneously converted into γ-lactones (XVIII) (Jones and Whiting, *J.*, **1949**, **1423**). On the other hand, if the esters are first oxidised to the γ-keto-esters (XIX), a simple process, nucleophilic

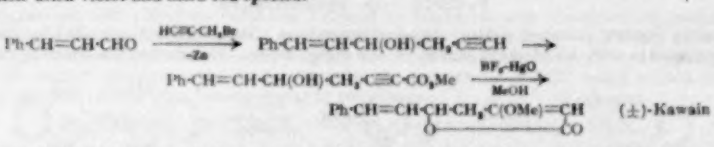
addition reactions occur in the reverse direction with the formation of α-substituted β-acylacrylic esters (XX).



By taking advantage of the nucleophilic addition reactions mentioned above, some progress has been made towards the synthesis of the plant-growth hormone, auxin-*b*, as formulated by Kögl and his collaborators (*Z. physiol. Chem.*, **1934**, **225**, 215). The *cyclo*pentenealdehyde (XXI), made by a route capable of extension to the more complex aldehydes required for the final auxin synthesis, is condensed with propargyl bromide by a Reformatsky reaction, and the resulting βγ-acetylenic carbinol is carboxylated. Addition of piperidine to the acetylenic linkage of the ester, followed by mild acid hydrolysis, yields the β-keto-ester (XXII) in excellent yield.



Hydrolysis of this ester with dilute sodium hydroxide solution, followed by acidification, leads to the lactone (XXIII), the conversion of which into the corresponding acid is at present being studied (Jones and Whiting, *J.*, **1949**, **1419**; Brown, Henbest, and Jones, unpublished). Mention should be made at this stage of Raphael's elegant syntheses of dihydropenicillic acid and of penicillic acid itself (*J.*, **1947**, 805; **1948**, 1508), both of which are based on reactions of the hydroxy-acetylenic acids. A synthesis of (±)-kawain has recently been achieved (Fowler, Henbest, and Jones, unpublished) by the application of similar reactions according to the accompanying scheme; the relationship of the synthetic material to the naturally-occurring lactone, (+)-kawain (Borsche and Peitzsch, *Ber.*, **1930**, **63**, 2414) being established by the identity of their ultra-violet and infra-red spectra.



Ethylenic linkages result from the partial hydrogenation of acetylenic bonds and, since isomerisations are unlikely to occur during hydrogenation, this procedure has distinct advantages over most others for the synthesis of ethylenic compounds containing the –CH=CH– grouping. Moreover, the partial catalytic hydrogenation of an isolated acetylenic linkage is stereo-selective, that is, it gives rise mainly to the *cis*-configuration of the resulting ethylenic bond. This almost exclusive production of the *cis*-isomer and the unequivocal position of the ethylenic bond are valuable advantages accruing from the partial hydrogenation procedure; moreover, in the majority of the naturally occurring unsaturated fatty acids, the *cis*-orientation is found. It is not surprising therefore, to find several examples in which this procedure is utilised. It should be noted that transformation into the *cis*-form is not absolutely quantitative: some complete hydrogenation occurs and traces of the *trans*-isomer may be present. However, the isolation of pure *cis*-forms is relatively simple when crystallisable materials are being employed.

In the synthesis of unsaturated lactones already referred to, lactonisation is possible only as a result of the *cis*-orientation of the double bond; in this case any *trans*-acid is eliminated on distillation. Lauer and Gensler (*J. Amer. Chem. Soc.*, **1945**, **67**, 1171) have achieved the synthesis of the *cis*-form of the plant-growth hormone, traumatic acid, by partial hydrogenation

of the corresponding acetylenic dicarboxylic acid. The synthesis of *cis*- and *trans*-octadec-11-enoic acids (Akmad, Bumpas, and Strong, *J. Amer. Chem. Soc.*, 1948, **70**, 3391, *cf.* 1699) illustrates

$$HC{\equiv}C{\cdot}[CH_2]_8{\cdot}CO_2H \xrightarrow[+\ CO_2]{Na\ salt} HO_2C{\cdot}C{\equiv}C{\cdot}[CH_2]_8{\cdot}CO_2H \xrightarrow[Ni]{H_2} HO_2C{\cdot}CH{=}CH{\cdot}[CH_2]_8{\cdot}CO_2H$$

cis-Traumatic acid.

clearly the potentialities for syntheses in the fatty acid series. Alkylation of oct-1-yne with a polymethylene chloride iodide leads to the chloro-alkyne and treatment of this with sodium cyanide suffices to provide the required carbon skeleton. Partial hydrogenation produces the *cis*-acid, which, on heating with selenium gives the *trans*-isomer. Mention should also be made

$$C_6H_{13}{\cdot}C{\equiv}CH + I{\cdot}[CH_2]_9{\cdot}Cl \xrightarrow[NH_3]{Na\text{-liq.}} C_6H_{13}{\cdot}C{\equiv}C{\cdot}[CH_2]_9{\cdot}Cl \xrightarrow[hydrol.]{NaCN\ and} C_6H_{13}{\cdot}C{\equiv}C{\cdot}[CH_2]_9{\cdot}CO_2H \xrightarrow[Pd]{Ni\text{-}H_2} (cis\text{-})C_6H_{13}{\cdot}CH{=}CH{\cdot}[CH_2]_9{\cdot}CO_2H \xrightarrow{Se,\ heat} trans\text{-}\ (vaccenic\ acid)$$

of the syntheses of geometrical isomerides of the naturally occurring insecticide, pellitorine, and the homologous herculin (Raphael and Sondheimer, *Nature*, 1949, **164**, 707), and of syntheses of alkenylphenols related to the constituents of cashew nut shell liquid and urushiol, the vesicant principle in poison ivy (Sletzinger and Dawson, *J. Org. Chem.*, 1949, **14**, 849; Wasserman and Dawson, *ibid.*, 1943, **8**, 73). An interesting extension of these methods is to be found in the recent work of Raphael and Sondheimer (*Nature*, in the press) on the synthesis of linoleic acid, presumably in the *di-cis*-form. The final product has as yet been obtained only in small

$$C_6H_{11}{\cdot}C{\equiv}CH \longrightarrow C_6H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH \longrightarrow C_6H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OMs \xrightarrow{EtMgBr}$$

$$Cl{\cdot}[CH_2]_6{\cdot}Cl \longrightarrow I{\cdot}[CH_2]_6{\cdot}Cl \longrightarrow HC{\equiv}C{\cdot}[CH_2]_6{\cdot}Cl$$

$$C_6H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}[CH_2]_6{\cdot}Cl \xrightarrow{CH_2(CO_2Et)_2}$$

$$C_6H_{11}{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[CH_2]_7{\cdot}CO_2H \xleftarrow[-CaCO_3]{H_2\text{-}Pd} C_6H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}[CH_2]_6{\cdot}CH_2{\cdot}CO_2H$$

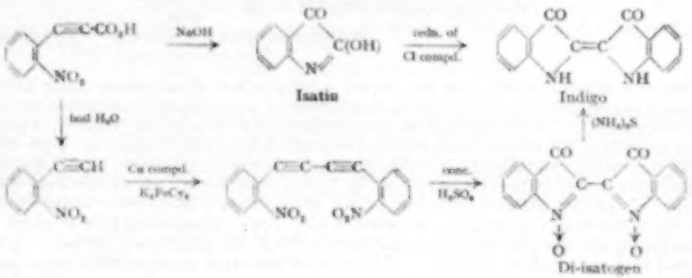
Linoleic acid — m. p. 43°

quantity but it gave a tetrabromide with the correct melting point. In view of the freedom from double-bond migration, procedures of this type may well prove to be particularly suitable for the synthesis of the rather unstable acids of the drying-oil type.

In 1870, Glaser (*Annalen*, **154**, 159) made the surprising observation that, when the copper derivative of phenylacetylene was oxidised with air in ammoniacal alcoholic solution, a smooth

$$Ph{\cdot}C{\equiv}CH \longrightarrow Ph{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}Ph$$

coupling reaction occurred yielding diphenyldiacetylene. This work was extended by Baeyer in connection with his classical studies in the indigo series. He effected the coupling of the



copper derivative of *o*-nitrophenylacetylene with potassium ferricyanide and converted the di(nitrophenyl)diacetylene with sulphuric acid into di-isatogen and thence produced indigo by reduction with ammonium sulphide. These experiments provided the first real evidence of the nature of the carbon skeleton of indigo (Baeyer, *Ber.*, 1880, **13**, 2254; 1882, **15**, 50).

The coupling reaction has been extensively studied and it has recently been shown, contrary

to the experiences of earlier workers, that the coupling of ethynylcarbinols by the convenient procedure of aerial oxidation in the presence of cuprous ammonium chloride is a general reaction, applicable to carbinols of various types (Bowden, Heilbron, Jones, and Sargent, *J.*, 1947, 1579). Furthermore, the function of the cuprous salt appears to be largely catalytic and considerably less than one equivalent can be employed.

The application of this oxidative coupling in the case of pentenynol (XXIV) to give the glycol (XXV) in 70% yield (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586) gives an indication of the scope of the method. Mixed coupling reactions cannot easily be effected in this way but it is worthy of note that Baeyer and Landsberg (*Ber.*, 1882, **15**, 57) obtained a good yield of

(XXIV.) $2HC{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH \longrightarrow HO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ (XXV.)

o-nitrodiphenyldiacetylene by treating a mixture of phenylacetylene and nitrophenylacetylene with ammoniacal cuprous chloride and oxidising the mixed copper salts with potassium ferricyanide. Such mixed coupling reactions are better carried out, however, by interaction of acetylenic Grignard reagents with iodoacetylenes (Grignard and Perichon, *Ann. Chim.*, 1926, **5**, 5; Horn and Weedon, forthcoming communication).

By oxidation of secondary ethynylcarbinols in acetone solution with chromic acid, the highly reactive ethynyl ketones (*e.g.*, XXVI) are readily prepared (Bowden, Heilbron, Jones, and

$Ph{\cdot}CH(OH){\cdot}C{\equiv}CH \longrightarrow Ph{\cdot}CO{\cdot}C{\equiv}CH$ (XXVI.)

Weedon, *J.*, 1946, 39). These substances undergo with notable facility a variety of addition reactions, and those with amines and other nucleophilic reagents, and with dienes, have been studied in some detail (Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45; Bowden and Jones, *J.*, 1946, 52; Bowden, Braude, and Jones, *J.*, 1946, 953). Application of the selective oxidation procedure to primary acetylenic alcohols yields the corresponding acids, and even the unsaturated glycol (XXV) can be oxidised smoothly to the dicarboxylic acid (XXVII) (Heilbron, Jones, and Sondheimer, *J.*, 1949, 604).

$(XXV) \longrightarrow HO_2C{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CO_2H$ (XXVII.)

Kuhn and Wallenfells (*Ber.*, 1938, **71**, 1510, 1889) achieved conspicuous success in the synthesis of polyenes and cumulenes *via* acetylenic glycols. From the 1 : 4- and 1 : 6-glycols, obtained by condensation of carbonyl compounds with acetylene and diacetylene, partial

$$Ph{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}CH{=}CHPh \xrightarrow{Pd\text{-}H_2}$$
$$Ph{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH{=}CHPh \longrightarrow Ph{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CHPh$$
(XXVIII.)

hydrogenation with palladium catalysts, followed by treatment with phosphorus di-iodide or chromous or vanadous chlorides, gave good yields of diphenylpolyenes (*e.g.*, XXVIII). On the other hand, direct reduction of the glycols with chromous chloride in the presence of hydrogen chloride yielded cumulenes, the scarlet tetraphenylhexapentaene (XXIX) being formed from the diacetylenic glycol from benzophenone in 90% yield.

$Ph_2C(OH){\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C(OH)Ph_2 \longrightarrow Ph_2C{=}C{=}C{=}C{=}C{=}CPh_2$ (XXIX.)

Not unrelated to these studies are some investigations carried out during the past year on the preparation of the conjugated poly-ynes, compounds containing a series of conjugated acetylenic linkages. The diacetylenes or di-ynes of this type are of course well known, being readily available by the coupling reaction already described. As long ago as 1885, Baeyer (*Ber.*, 18, 674, 2269) conceived the idea of making a conjugated tetra-acetylenic compound by the coupling of diacetylenecarboxylic acid, $HC{\equiv}C{\cdot}C{\equiv}C{\cdot}CO_2H$, but the product proved to be extraordinarily unstable although on reduction with sodium amalgam he did obtain a small amount of what might have been sebacic acid.

In seeking general methods we directed our attention to the observation that 1 : 4-dichlorobut-2-yne (XXX), prepared from the easily accessible butynediol with thionyl chloride, yields diacetylene on treatment with alkaline reagents (cf. Keyssner and Eichler, G.P. 750,637; Johnson, *J.*, 1946, 1009, 1014). It has now been found (Armitage, Jones, and Whiting, unpublished) that, when this process is carried out with sodamide in liquid ammonia, either the mono- or the di-sodio-derivative of diacetylene can be obtained at will, practically instantaneously and in quantitative yields. The ready production of the monosodio-derivative is particularly important since by straightforward substitution reactions, carried out subsequently in the

liquid ammonia medium, mono-substituted diacetylenes (XXXI) can easily be made. Already we have observed that these substances can be coupled by the standard methods to yield the conjugated tetra-acetylenes or tetra-ynes (XXXII).

$$\underset{\text{(XXX.)}}{ClCH_2{\cdot}C{\equiv}C{\cdot}CH_2Cl} \xrightarrow[\text{liq. } NH_3]{NaNH_2} NaC{\equiv}C{\cdot}C{\equiv}CH \longrightarrow \underset{\text{(XXXI.)}}{R{\cdot}C{\equiv}C{\cdot}C{\equiv}CH} \xrightarrow{EtMgBr\text{-}I_2} \underset{\text{(XXXII.)}}{R{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}R}$$

If the disodio-derivative, in the liquid ammonia in which it is formed, is treated with formaldehyde, then hexadiynediol (XXXIII) is produced in almost 90% yield. This can be

$$NaC{\equiv}C{\cdot}C{\equiv}CNa \xrightarrow{CH_2O} \underset{\text{(XXXIII.)}}{HO{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH} \xrightarrow[C_5H_5N]{SOCl_2}$$

$$ClCH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2Cl \xrightarrow[\text{liq. } NH_3]{NaNH_2} NaC{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}CNa \xrightarrow{MeI} Me{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}CMe$$

converted into the dichloride, and by repetition of the sodamide treatment the sodio-derivatives of triacetylene are obtained, and its mono- and di-alkyl derivatives and other condensation products thus become available.

It is not possible at this stage to give more than a brief description of the properties of these novel substances, the parents of which are the polyacetylene hydrocarbons, C_nH_2. Considerable differences have been observed between individual members and, although in general they appear to be rather unstable under normal conditions, in nitrogen or in a vacuum at $-70°$ they can be kept for reasonable periods. Dimethyltriacetylene (1 : 6-dimethylhexatriyne) crystallises well and has m. p. 128°, and dimethyltetra-acetylene (1 : 8-dimethyloctatetrayne), which is also beautifully crystalline, decomposes when heated above about 80°. The ultra-violet light absorption properties of the tetra-acetylenes have revealed some unexpected features, especially the remarkably high intensity of the absorption in the 2200—2500-A. region. The intensities, ε = about 270,000, which have been observed in several cases, are amongst the highest ever recorded. Now that methods of synthesis have been developed, it is hoped to examine the physical properties of a wide range of substances of this polyacetylene series, since the enforced linearity of the conjugated poly-yne chain might be expected to endow these predominantly carbon-containing molecules with exceptional properties.

Acetylene has frequently been employed in synthetic work mainly as a convenient and reactive unit for building up the required carbon skeletons. The scope for the use of acetylenic compounds in synthesis is, however, by no means restricted to this purpose, and in many of the cases already discussed due advantage has been taken of the well-known and unique addition reactions of the triple bond in order subsequently to introduce functional groups. No attempt can be made here to summarise these addition reactions, but some recently discovered procedures which break new ground merit special attention.

The first of these concerns the conversion of ethynyl compounds into aldehydes. It has long been known that methyl ketones or their derivatives result from the catalysed hydration of compounds containing an ethynyl group; attempts have been made to obtain aldehydes by reversing the direction of hydration but such successes as have been claimed have been shown

$$R{\cdot}CH_2{\cdot}CHO \longleftarrow R{\cdot}C{\equiv}CH \longrightarrow R{\cdot}CO{\cdot}CH_3$$

to be largely ill-founded (for summary, cf. Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244). It has now been found that when thiolacetic acid reacts with monosubstituted acetylenes, under the influence of organic peroxides or irradiation with ultra-violet light, mono- and di-adducts are produced by " abnormal " addition reactions. The mono-adducts on treatment with the usual carbonyl reagents are converted smoothly into derivatives of the corresponding aldehydes, while,

$$Bu{\cdot}C{\equiv}CH \begin{cases} \rightarrow Bu{\cdot}CH{=}CH{\cdot}SAc \xrightarrow{NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2} [Bu{\cdot}CH{=}CH{\cdot}SH] \longrightarrow Bu{\cdot}CH_2{\cdot}CH{=}N{\cdot}NH{\cdot}CO{\cdot}NH_2 \\ \quad + \\ \rightarrow Bu{\cdot}CH(SAc){\cdot}CH_2{\cdot}SAc \longrightarrow Bu{\cdot}CH(SH){\cdot}CH_2{\cdot}SH \end{cases} \qquad \downarrow \qquad Bu{\cdot}CH_2{\cdot}CHO$$

under rather more acidic conditions, the di-adducts yield 1 : 2-dithiols (Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619; cf. Behringer, *Annalen*, 1949, **564**, 219).

Another elegant method of obtaining aldehydes *via* acetylenic compounds has been described by Arens and Van Dorp (*Nature*, 1947, **160**, 189; *Rec. Trav. chim.*, 1948, **67**, 973) in connection with their important synthetic work in the vitamin A series. These authors found that the

carbinols arising from condensation of ethoxyacetylene with carbonyl compounds gave, after partial hydrogenation, ethylenic carbinols convertible by mild treatment with dilute acids into

$$>C{=}O \longrightarrow >C(OH){\cdot}C{\equiv}C{\cdot}OEt \xrightarrow{H_2} >C(OH){\cdot}CH{=}CH{\cdot}OEt \xrightarrow{\text{acids}} >C{=}CH{\cdot}CHO$$

αβ-unsaturated aldehydes. The last stage in this procedure is analogous to the behaviour of certain β-chlorovinylcarbinols under similar conditions (Jones and Weedon, *J.*, 1946, 937).

Finally, the discovery by Reppe and his collaborators (B.I.O.S. Final Reports Nos. 266, 355, and 358; see also *Experientia*, 1949, **5**, 93) of a method of effecting the combination of acetylenic compounds and carbon monoxide provides an outstanding additional rôle to the already extensive repertoire of the acetylenic bond in synthetic operations. Using nickel carbonyl, either stoicheiometrically or, together with carbon monoxide, as a catalyst, in reactions either with acetylene itself or with simple acetylenic hydrocarbons, Reppe succeeded in obtaining acrylic acid and related substances. This novel reaction thus leads to syntheses of branched-

$$R{\cdot}C{\equiv}CH \xrightarrow[H_2O]{CO} R{\cdot}\underset{CO_2H}{\overset{}{C}}{=}CH_2 \qquad R{\cdot}CH(OAc){\cdot}\underset{CO_2H}{\overset{}{C}}{=}CH_2 \qquad \text{(XXXIV.)}$$

chain compounds by addition to the triple bond, a possibility realised hitherto only in a few instances such as the application of the Michael reaction to αβ-acetylenic carbonyl compounds (*e.g.*, Dey, *J.*, 1937, 1057). Much careful study has been necessary in order to find suitable conditions for the extension of this reaction to acetylenic carbinols but, by employing the acetates of the carbinols in reactions with nickel carbonyl in alcohol–acetic acid media, reasonable conversions into analogues (XXXIV) of acrylic acid have been achieved. From the βγ-acetylenic carbinols, the hitherto practically inaccessible methylenebutyrolactone (XXXV), a naturally-

$$HO{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH \longrightarrow \underset{O\text{——}CO}{\overset{}{CH_2{\cdot}CH_2{\cdot}C}}{=}CH_2 \qquad \text{(XXXV.)}$$

occurring antibiotic (Cavallito and Haskell, *J. Amer. Chem. Soc.*, 1946, **68**, 2332), has been synthesised in this way (Jones, Shen, and Whiting, *J.*, in the press).

It is usual at this stage, when so much collaborative work has been described, for some tribute to be paid to those who, by their efforts, have contributed to the development of the subject. Although my remarks must, of necessity, be brief, I do not pay this tribute in any perfunctory spirit, but rather with a deep and sincere feeling of gratitude for the wholehearted co-operation and assistance which it has been my good fortune to receive. It is a source of much pleasure to note that several of our former co-workers are actively engaged in exploring and exploiting new territories in the vast realm which is acetylene chemistry.

To you, Mr. President, in your rôle as teacher, colleague, and friend, and to our many collaborators, both past and present, to whom most of the credit is due, I offer my warmest thanks.

OBITUARY NOTICE.

ALEXANDER SCOTT.

1853—1947.

[Abridged, by permission, from the Notice by the late Sir Robert Robertson in *Obituary Notices of Fellows of the Royal Society*, **1948**, **6**, 251—262.]

On 10 March 1947, at the great age of ninety-three, Dr. Alexander Scott, inorganic chemist, died at Ringwood, Hampshire. He was born in the county town of Selkirk on 28 December 1853, the son of Alexander Scott and the eldest of a family of four sons and four daughters, some of whom are now living.

The family appears to have migrated from the Scott Border country, for there are records of forebears being settled in Fife, in Kilconquhar or its neighbourhood, in the middle of the eighteenth century, evidently as farmers.

It was thus a return to the Scott country that the father of the subject of this Notice made when he was appointed Rector of Selkirk Academy in 1851, a post he held for thirty-three years. He was also Kirk Session Clerk for twenty-eight years and an Elder for nine. To a testimonial in 1883, one hundred and sixty-five of his former pupils put their names and among these is Andrew Lang, who was Selkirk-born. It is however as a botanist that the Rector had the greatest influence over his son, for he was a field botanist of repute, identifying wild plants scientifically by the Flora and making excursions after the rarer kinds. Not only had this a profound effect on the son as is shown by his love of flowers, by his choice of botanists as friends and by his selection of plants in his London garden, but in the opinion of the writer, who has had a similar fortunate experience, it was an early introduction to practice in scientific method.

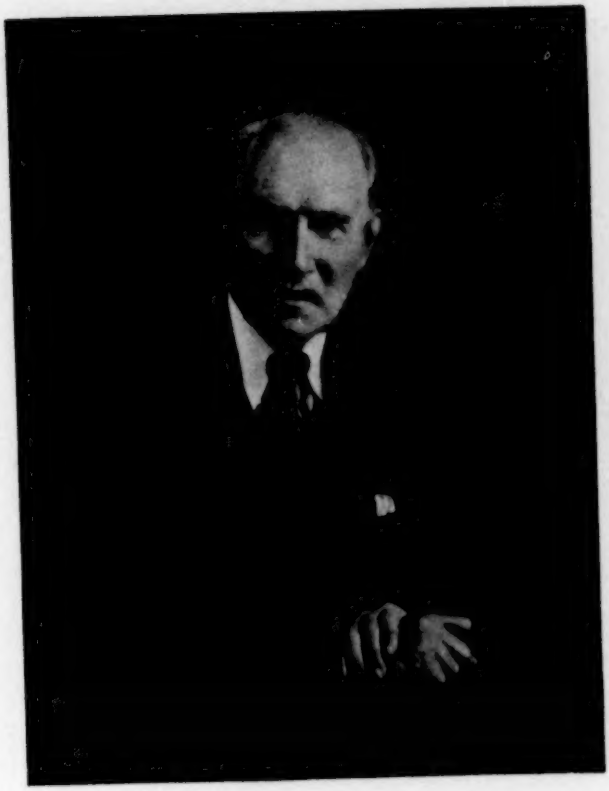
In those days it was the custom to send boys to the University at an age which seems to us somewhat immature. Accordingly, young Scott matriculated at Edinburgh University in November 1868 at the age of fifteen. At first he had the idea of becoming an engineer, and towards this end studied under Tait and Fleeming Jenkin. Nor was botany neglected, for he attended the lectures of Balfour who had brought from the school of Sachs physiological botany, a supplement to the field botany in which he had been hitherto interested. These studies were, however, soon subordinated to chemistry when he came under the influence of Crum Brown and of Dewar. Crum Brown not only devoted himself to those questions of structural chemistry with which we associate him, but ran large classes of over a hundred. It was a source of pleasure to Scott that in such a class he had the distinction of being Senior Medallist. In 1876 he graduated B.Sc. in Experimental Philosophy, his Doctorate following in 1884 with a thesis "On the atomic weight of manganese." During this time, as also later, he was noted for his phenomenal knowledge of the materials of inorganic chemistry.

From 1872 to 1875 Dewar was lecturer at the Dick Veterinary College and Scott was his student assistant.

In 1875 Dewar was elected Jacksonian Professor of Natural Experimental Philosophy at Cambridge, whither Scott followed him in the same year, having been appointed assistant to the Jacksonian Professor. Here he lectured on physical and organic chemistry and supervised advanced students engaged in research. In 1876 he obtained a Clothworkers' Exhibition in physical science, and in 1878 a Foundation Scholarship in natural science at Trinity College. In 1879 he took his B.A. with first-class Honours in natural science, and graduated M.A. in 1882. He also examined for Tripos and other examinations.

Influenced by Dr. Fearon, the headmaster of Durham School, in June 1884, Scott undertook the entire management of the science teaching in Durham School in a new laboratory erected by the Governors under his supervision. He was further induced to make the change as opportunity of time for original research was offered. Later, in a new chemical and metallurgical laboratory erected and equipped under his direction at Middlesbrough, by the Trustees of the High School, he lectured to large classes—with great acceptance according to Sir Hugh Bell. Scott welcomed this opportunity of developing scientific teaching in the North of England, for, as he says in his first Presidential Address to the Chemical Society (1916), educational matters always interested him profoundly.

It was while here that Scott found the teaching of science in poor case, being handicapped by science masters either ill-trained or having to subordinate their efforts to preparing their pupils for answering the highly specialised questions of scholarship examinations. In the same



Alexander Scott

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[*To face p. 762.*

Presidential Address, the opportunity of successful careers for science students is compared with the rewards open to classical or mathematical students, and an appeal is made for a change of outlook.

Scott while at Durham must have led a strenuous life, for not only had he the supervision of the teaching of science at Durham and Middlesbrough schools, but he was busy at his experimental work, especially with his apparatus for determining the combining volumes of hydrogen and oxygen, towards which he received a grant from this Society, but in addition he found time to write a textbook, "Introduction to Chemical Theory," A. and C. Black, 1891, which ran into a second edition.

In 1891 Scott returned to Cambridge as Demonstrator to the Jacksonian Professor (Dewar) and took up the threads of his experimental work and his tutorial activities. As before, the main topic of his research was connected with the determination of accurate atomic weights, and between 1891 and 1896 he presented several papers and wrote reviews of the subject to the scientific press.

In 1877 Dewar had become Fullerian Professor of Chemistry at the Royal Institution. This Institution took over the Davy-Faraday Research Laboratory in 1896 by Deed of Trust from Dr. Ludwig Mond who had munificently bought the next-door premises, furnished them as laboratories and had put £62,000 aside for running expenses. The Laboratory was opened with much ceremony on 22 December 1896 by H.R.H. the Prince of Wales. It was designed to afford opportunities for skilled workers who had the wish and time to devote to the solution of important problems. All laboratory facilities but no emoluments were provided for the workers. Professor Dewar and the third Lord Rayleigh were appointed Directors, and Dr. Alexander Scott Superintendent of the Laboratory. Here Scott worked for fifteen years on the determination of the atomic weights of various elements and methods for the preparation of substances in a state of high purity, but his advice was frequently asked by the workers in the Laboratory, who included Horace T. Brown, H. Debus, A. Liversidge, A. Mallock, Hugo Müller, Joseph Petavel, Charles E. S. Phillips, P. C. Ray, W. J. Russell, G. Senter, and Henry T. Tizard. With these his relations were very amicable and he held the respect of the staff. As one of the workers of that time has said, Scott had a kindly friendliness to the sincere worker. He was intolerant of slip-shod work.

This went on till 1910 when it was decided by the Managers to terminate the office of Superintendent in 1911. This led to much acrimony between Scott and Dewar, as might be expected between two personalities of such individualistic and independent character.

In 1898 Scott was elected into the Royal Society.

Scott now worked in his own laboratory at Upper Hamilton Terrace and devoted much time to the affairs of the Chemical Society. After having been two years on the Council (1897—1899) he held the post of Secretary until 1904 when he became Treasurer and held this office until his Presidency (1915—1917). More systematic arrangements for the conduct of its business were made by Scott, and under his leadership the first steps were taken which led to the formation and incorporation of the Association of British Chemical Manufacturers, a body which has done much to secure a prosperous chemical industry and had itself provided assistance to the Chemical Society.

During this period Scott delivered two Presidential Addresses to the Chemical Society: the one (1916) containing a sketch of the history of the Society, Scott's views on research and his strictures on the outlets for chemists, referred to above, and the other (1917) dealing with the atomic theory and Prout's hypothesis.

A new interest was aroused when, in 1919, at the request of the Department of Scientific and Industrial Research, Scott conducted an inquiry into the condition of objects at the British Museum alleged to have suffered deterioration by storage in London's Underground during the 1914—1918 war. A small laboratory was established at the Museum on his recommendation, sanctioned by H.M. Treasury on the condition of its being a "purely temporary experiment to come to an end in three years." Here, under his supervision, a scientific study was made of ancient materials and their reactions to various environments, and methods of preservation and restoration were worked out and in due course published. How successful was the work done may be judged by the subsequent development of the laboratory idea in museums in general, by the eventual incorporation of the original laboratory as a separate department of the British Museum (recommendation of the Royal Commission on Museums) and by the views of the parent Department expressed at the time of transfer recording cordial appreciation of the distinguished service of Dr. Scott, "service which has enhanced very considerably the value of our National Collections and works of art."

He retired in 1938, aged 85, mentally as alert as ever and able to maintain the keenest interest in science and in museum work to the very end. He was beloved by his staff at the Museum, and for them will remain a great tradition, a symbol of the dignity of science and of mental vigour and integrity.

SCIENTIFIC WORK.

Attainment of the highest possible accuracy in the determination of the atomic weights of elements was the method, but the philosophical inquiry underlying Scott's work was as to whether Prout's hypothesis was true in fact.

In Dalton's Atomic Theory it is postulated that all the atoms of an element are similar and equal in atomic weight. For many years this was fully accepted by chemists, with one exception, that of Crookes who, in 1886, suggested the idea of the heterogeneity of atoms, a conception at that time and for many years after considered as highly speculative, but which was nevertheless true, for many years later Aston showed that atoms are accompanied by other atoms of similar chemical properties but of slightly different weight called isotopes, whose relative abundance settles the atomic weight as determined by analysis.

Founding his speculation on Dalton, Prout, an English chemist and physician, sent in to the *Annals of Philosophy* in 1815 and 1817, papers in which, with the values then available, he calculated that the weights of a number of elements were multiples of that of hydrogen; this he considered the πρώτη ὕλη of the Greek philosophers. The validity of this hypothesis was a matter of contention among chemists for a hundred years.

The obvious course was to ascertain if it was true in fact, and the quest proved a very potent stimulus to inquiry, especially demanding the most careful determination of atomic weights. To this end chemists applied themselves, striving after more and more accuracy by using greater and greater precautions. Various compromises were suggested, for example, halving the unit on account of the uncomfortable value of 35½ for chlorine, and even quartering it. Dumas, in 1842, by a method used earlier by Berzelius and Dulong, that of passing a stream of hydrogen over a weighed quantity of heated copper oxide and weighing the water produced, got a result showing that 2 parts of hydrogen are combined with 15·96 parts of oxygen, but Dumas, on the basis of Prout's hypothesis, assumed the ratio 2 : 16.

The chemists were divided as to the validity of Prout's hypothesis. When, in 1860, Stas, the superb experimenter, began his researches, he undertook them as he said, with " an absolute belief in the exactness of the principle of Prout," but in a few years, as a result of his own work, he took the view " that the hypothesis of Prout is a pure illusion."

In 1880, Mallet stated that out of eighteen elements, ten approximate to integers within a range of 0·1 unit, and remarked that " not only is Prout's Law not as yet absolutely overturned, but a heavy increasing weight of probability in its favour or in favour of some modification of it exists and demands consideration."

It was thus at a time when unequivocal values were required for atomic weights that Scott started, at first in Cambridge with Dewar, then extramurally by himself at Durham, then again alone at Cambridge and finally at the Royal Institution, to provide accurate atomic weights, always having in mind the need to test Prout's hypothesis.

Atomic Weight of Potassium and Sodium.—During 1875—1884 published papers are in the names of Dewar and Scott, and in the first of these were determinations of the vapour densities of potassium and sodium (1879), as a clue to their atomic weights. The Victor Meyer displacement method was used, and in the first instance the metals were vaporised in a heated iron pot. As difficulties arose from the action of the vapour on iron, this was then replaced by a platinum vessel in spite of the " terrible waste " of the metal. It is concluded that in the state of vapour potassium and sodium are monatomic, but this method does not, of course, provide precise atomic weights.

Atomic Weight of Manganese.—Determination of the atomic weight of manganese follows (1881), values having been reported varying from 54 to 55. As objections could be seen to the reagents used by previous workers, a new one was chosen—silver permanganate, a substance having the advantages of being obtained pure by crystallisation and also of not being hygroscopic. The first experiments, in which the salt was decomposed with loss of oxygen, gave discrepant results, but good ones were got by titrating the silver by an acid solution of potassium bromide, all the precautions laid down by Stas for this kind of work being observed. The mean of eight concordant experiments was 55·038, taking oxygen at 16 and Stas's value for silver 107·93. This is very near the most recent value adopted by the International Committee on Atomic Weights, 54·93 (Silver 107·88).

This piece of accurate work was put forward in Scott's thesis for D.Sc. of Edinburgh University (1883).

Composition of Water by Volume.—Time was found for his researches while in the North, and the paper (1888) on the composition of water by volume comes from his laboratory in Durham School. In a later paper on the same subject from Cambridge, he refers to this as a preliminary note on a subject on which no work has been done since the time of Gay-Lussac and Humboldt.

In Professor Partington's book on " The Composition of Water " (London, G. Bell & Sons, 1928) will be found a historical account of the earlier work on this subject by Cavendish, Lavoisier, Monge, Priestley, Gay-Lussac, and Humboldt and details are given of the experimental methods of Dumas, Morley, Scott, and Burt and Edgar. Partington quotes from Scott's paper (1894) : " Throughout I have endeavoured to use the simplest apparatus possible and to prepare the gases themselves from only the purest materials, and those of the simplest composition that I could find, so that no purification should be required and all unnecessary contact with other chemical substances avoided, to work with an apparatus of glass throughout, so that no diffusion could take place, and finally, so to work, that with a given amount of materials, I might compare the gas given off in the first fractions continuously to the last fractions, and thus endeavour to detect any possible impurity, either by variation of the ratio, or by actual observation from the residual gas."

Then follow descriptions of the sources of the hydrogen and of the oxygen, and a sketch of Scott's apparatus is reproduced. Partington remarks on the high degree of precision, very pure gases being used, the gases measured with great accuracy, their temperature and pressure being carefully controlled throughout the experiment, and the analysis of the residual gas being exact.

Examples of typical experiments are given in the paper, and the ratio of oxygen to hydrogen by volume is found to be 1 : 2·0045 at temperatures of 14° to 18°, both gases being measured at the same temperature. If, however, the values for the coefficient of expansion of oxygen and hydrogen are taken into account the value of 2·00285 at 0° is found for the ratio of the combining volumes. This value, combined with the value 15·882 for the ratio of densities found by Lord Rayleigh, gives the atomic weight of oxygen 15·862, and, if oxygen is taken as 16, of hydrogen 1·008, the present accepted figure being 1·0078.

In a very accurate series of experiments in 1915 Burt and Edgar made use of facilities not available to Scott, and measured the gases actually at 0° and 1 atm., thus avoiding the correction for expansion. They obtained for the above ratio 1 : 2·00288.

Atomic Weight of Carbon.—In a review of the various determinations of the atomic weight of carbon (1897), Scott called attention to discrepancies among these and indicated possible sources of error. Already Dewar and Scott (1883) had employed another method—that of titrating with silver the bromine in the hydrobromide of triethylamine, but the results were disappointing on account of the difficulty of getting pure triethylamine together with a slight tendency of its hydrobromide to hydrolyse.

Scott returns to the subject (1909) when he uses the elegant method of titrating tetra-alkylammonium bromides, choosing these because of their relatively stable character and easy purification. This paper gives the details of his experiments on titrating tetra-alkylammonium bromide with silver and, with the same silver, ammonium bromide. By subtraction the equivalent of a hydrocarbon C_4H_{14} is derived. Thus with silver at 107·88, the atomic weight of carbon is found to be 12·017 from tetramethylammonium bromide, the present accepted figure being 12·010, silver being 107·880.

By another method in which carbon monoxide and oxygen were exploded in the apparatus used for determining the composition of water by volume (1894) a value of 11·99 was deduced for carbon (1904).

From a few experiments (1909) on the combustion of naphthalene and of cinnamic acid, the value of the atomic weight of carbon comes out at C = 12·00. " The cause of the discrepancy between these results and those derived from the alkylammonium bromides remains still to be discovered."

Atomic Weight of Nitrogen.—By the titration of ammonium chloride and bromide against silver Scott obtained results lower than those of Stas, and this has been confirmed especially by Lord Rayleigh and by Whytlaw-Gray who, using nitric oxide (*J.*, 1905, **87**, 1601), obtained 14·01, practically the same value as Scott. The most recent International Tables give N = 14·008.

Atomic Weight of Tellurium.—This is described as a preliminary notice (1902) and has the object of confirming the value for the atomic weight of tellurium, which has an anomalous

position in the Periodic Table in being higher than that of iodine. Scott's method was to make careful determinations of the halogens in the stable salts trimethyltellurium bromide and iodide. Taking the values O = 16, C = 12·00, H = 1·0075, I = 126·85 and Br = 79·95 tellurium was found to have an atomic weight of 127·7, the value given in the recent tables being 127·61. Tellurium with its abundance and range of isotopes thus occupies an anomalous position in the Periodic Table with regard to iodine which has none.

Other Papers.—These are either of general interest such as a new series of mixed sulphates of the vitriol group (1897), a new sulphide of arsenic (1900), the vapour density of hydrazine hydrate (1904), correction of weighings in air to vacuum (1909); or are descriptions of methods for preparing substances used in determination of atomic weight, such as preparation of pure hydrobromic acid (1900), of alkyl derivatives of sulphur, selenium, and tellurium (1904), and of pure bromine (1913).

Services to Art and Archæology. (By Dr. H. J. Plenderleith.)—Scott's contribution to the problems of art and archæology was characteristically that of the experimenter and teacher rather than the writer of textbooks, and his aim was to discover and publish simple methods of treatment that would be safe in the hands of those not having the advantage of a technical or scientific background.

A great source of inspiration was his visit to Luxor for the winter season (1923—1924) at the invitation Howard Carter to act as consulting chemist in devising methods of preserving the objects from Tut-Ankh-Amun's tomb. It was this intimate study of antiquity in the field in all its frail beauty and the confidence that science had so much to contribute that provided him with the incentive to create a permanent scientific service in the the British Museum.

If primarily concerned with the problems of metallic corrosion or saline incrustations in exhumed material, work at the British Museum soon developed important off-shoots scarcely to be anticipated in the early days. For example, a body of knowledge was gradually acquired which could be applied to differentiate the genuine antiquity from the false or to classify types of ethnic culture and solve problems of age and provenance. The value of such work could be assessed in terms understood and appreciated by H.M. Treasury. Once established on a permanent basis it was possible to afford unstinting help to other institutions, museums, libraries and picture galleries.

It was not to be expected that intricate operations would be undertaken by a man of his years; what was of lasting value was the standing that science was given in museum and gallery circles by his great knowledge, his strong personality and his genius for friendship in all walks of life. His advice was sought from every quarter of the civilised world and freely and promptly given wherever it would be of value in the interests of art, archæology or science.

This was his contribution: to represent science as the servant of the arts, to disarm suspicion where it existed, to demonstrate what might by this fruitful liaison be achieved and thus to lay the foundation for a partnership between art and science of mutual benefit for all time.

Alexander Scott died at Ringwood, Hampshire, on 10 March 1947. In 1906 he married Agnes Mary, daughter of Dr. W. J. Russell, F.R.S., and leaves no family.

In the preparation of this Notice, I have been indebted to Dr. Scott's widow and his family for biographical material, and very notably to Dr. H. J. Plenderleith, Scott's successor as Director of the British Museum Laboratory, for his contribution on the period 1919 to 1938, and for his appreciation of Scott's "Services to Art and Archæology."

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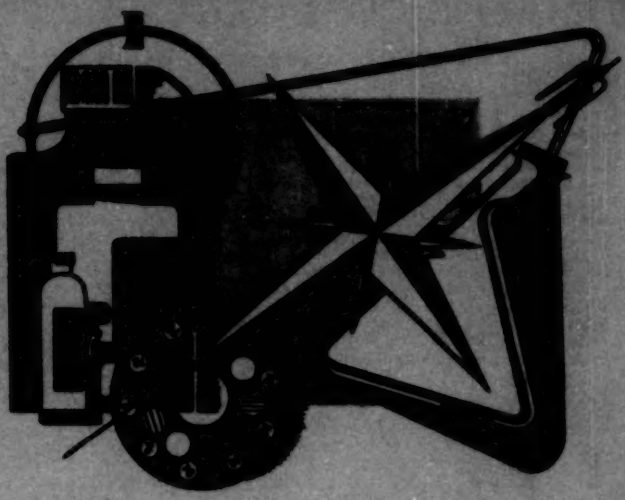

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